

Review

Colorectal endoscopic submucosal dissection: Technical advantages compared to endoscopic mucosal resection and minimally invasive surgery

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Background and Aim: In recent years, the effectiveness of colorectal endoscopic submucosal dissection (ESD) has been increasingly reported. Herein, we highlight the most recent developments and technical advantages of colorectal ESD compared to EMR and minimally invasive surgery.

Methods: All candidate lesions for ESD were confirmed as being intramucosal tumors by colonoscopy. Presently, the indications for colorectal ESD approved by the Japanese government's medical insurance system are early colorectal cancers with a maximum tumor size of 2–5 cm; however, many early cancers >5 cm have been treated by ESD in referral centers.

Results: The primary advantage of ESD compared to endoscopic mucosal resection (EMR) is a higher en-bloc resection rate for large colonic tumors that had previously been treated by surgery. ESD has several advantages compared to other therapeutic modalities, such as being a safer technique and providing

better quality of life. For rectal cancer treatment, a longer procedure time is required for laparoscopic assisted colectomy, whereas trans-anal resection and trans-anal endoscopic microsurgery are more invasive than ESD with a significantly higher recurrence rate. Accordingly, ESD is the preferred choice for early colorectal cancers when there is no risk of lymph-node metastasis.

Conclusion: ESD is an effective procedure for treating non-invasive non-polypoid colorectal tumors. These tumors may be difficult to resect en bloc by conventional EMR. The use of ESD results in a higher en-bloc resection rate and is less invasive than surgery.

Key words: colorectum, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), laterally spreading tumor granular type (LST-G), laterally spreading tumor non-granular type (LST-NG)

INTRODUCTION

ENDOSCOPIC MUCOSAL RESECTION (EMR)^{1–5} is indicated for the treatment of colorectal adenomas, intramucosal and submucosal superficial cancers (SM1; invasion <1000 μm from the muscularis mucosae) because of the negligible risk of lymph-node (LN) metastasis⁶ and excellent clinical outcome.^{2–4}

Endoscopic submucosal dissection (ESD) is accepted as a standard minimally invasive treatment for early gastric^{7,8} and esophageal cancers in Japan, Korea and some Western countries. Yamamoto *et al.*⁹ and Fujishiro *et al.*¹⁰ first started carrying out colonic ESD in the late 1990s, but such procedures

were being conducted by a limited number of specialists only.^{9–11} As a result of the widespread acceptance of gastric and esophageal ESD, the number of medical facilities carrying out colorectal ESD has been growing and its effectiveness has been increasingly reported in recent years.^{12–17}

However, this procedure is seldom carried out in Western countries because of technical difficulty, lack of comparative outcomes and the associated health-care costs between different modalities of treatment. Consequently, further technical advances and the availability of a suitable clinical training system are required for the extensive use of colorectal ESD. In this review, we highlight the most recent developments and technical advantages of colorectal ESD compared to EMR and minimally invasive surgery.

Indications for colorectal ESD

Presently, the indications for colorectal ESD approved by the Japanese government's medical insurance system are

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Table 1 Indications for colorectal ESD at National Cancer Center Hospital

| Non-invasive pattern should be diagnosed by chromo-magnification colonoscopy | | | | |
|--|--------|-------------|------------------------|------------------------|
| Tumor size (mm) | <10 | 10–20 | 20–30 | >30 |
| 0-IIa, IIc, IIa+IIc (LST-NG) [†] | EMR | EMR | ESD candidate | ESD candidate |
| 0-Is+IIa (LST-G) [‡] | EMR | EMR | EMR | Possible ESD candidate |
| 0-Is (villous) [§] | EMR | EMR | EMR | Possible ESD candidate |
| Intramucosal tumor with non-lifting sign [¶] | EMR | EMR/ESD | Possible ESD candidate | Possible ESD candidate |
| Rectal carcinoid tumor ^{††} | ESMR-L | ESD/Surgery | Surgery | Surgery |

Non-invasive pattern diagnosed by chromo-magnification colonoscopy.

[†]0-IIa, IIc, IIa+IIc (laterally spreading tumor non-granular type: LST-NG) > 20 mm.

[‡]0-Is+IIa (LST granular type: LST-G) > 30 mm.

[§]0-Is (villous) > 30 mm.

[¶]Intramucosal tumors with non-lifting sign which are difficult to resect en-bloc by conventional EMR.

^{††}Rectal carcinoid tumors <1 cm in diameter can be treated by endoscopic submucosal resection using a ligation device (ESMR-L) simply, safely and effectively, so not an indication for ESD.

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

colorectal adenomas and cancers with a maximum tumor size of 2–5 cm, taking into account the procedure's technical standardization and safety throughout Japan.¹⁸

Indications for colorectal ESD at the National Cancer Center Hospital

Table 1 shows the indications for colorectal ESD at the National Cancer Center Hospital (NCCCH). Based on our previous clinicopathological analyses of laterally spreading tumors (LST),^{4,19} LST non-granular type (LST-NG) lesions have a higher rate of submucosal (SM) invasion, which can be difficult to predict endoscopically (Figs 1,2). Approximately 30–56%²⁰ of LST-NG have multifocal SM invasion, which is primarily SM superficial (SM1). This is especially difficult to predict before endoscopic treatment. However, LST granular type (LST-G) lesions have a lower rate of SM invasion, which is generally found under the largest nodule or depression. These lesions are easier to predict endoscopically.^{4,19} LST-G >20 mm can be treated by elective piecemeal EMR rather than by ESD. The area containing the largest nodule should be resected before resection of the remaining tumor.

LST-G >30 mm are possible candidates for ESD as such lesions are more difficult to treat by piecemeal EMR (Figs 3,4). We previously reported a high SM invasion rate and a 25% rate of multifocal invasion,²⁰ compared to other recent series.^{21,22} The endoscopist's skill level and the duration of the resection should also be considered when selecting ESD for large lesions ≥5 cm. 0-IIc lesions >20 mm, intramucosal tumors with non-lifting sign and large sessile lesions, all of which are difficult to resect en bloc by conventional EMR, are also potential candidates for colorectal ESD.

Treatment of residual and recurrent tumors with ESD can be considered, depending on the circumstances. Such lesions usually involve severe fibrosis; therefore, they are not good candidates unless they are located in the lower rectum where the risk of perforation is very low.²³ Rectal carcinoid tumors measuring <1 cm in diameter are not considered an indication for ESD, as they can be treated by endoscopic submucosal resection using a ligation device (ESMR-L) safely, effectively and easily.^{24,25}

METHODS OF ESD

Equipment used in ESD

Endoscope system

An endoscope system with water jet function is preferable.

ESD knives

Various electrosurgical knives have been developed as follows. Flex knife (KD-630L; Olympus, Tokyo, Japan),¹⁰ Hook knife (KD-260R; Olympus),^{13,26} Flush knife (DK2618JN; Fujifilm, Tokyo, Japan),¹⁴ B-Knife™ (Zeon Medical, Tokyo, Japan)^{27,28} and Mucosectom® (Pentax, Tokyo, Japan). Dual knife (KD-650Q; Olympus) is an improved version of the Flex knife.

The Flush knife¹⁴ has the additional advantage of allowing local injection in the same device. A Flush knife ball-tipped (BT) type (DK2618JB; Fujifilm) has been developed to improve the hemostatic function of the standard model.

The B-Knife is a bipolar diathermy knife that results in safer procedures by reducing the risk of perforation.^{27,28} The ball-tip B-knife with water jet function (Jet B-knife) (XEMEX Co., Tokyo, Japan) has recently become available.

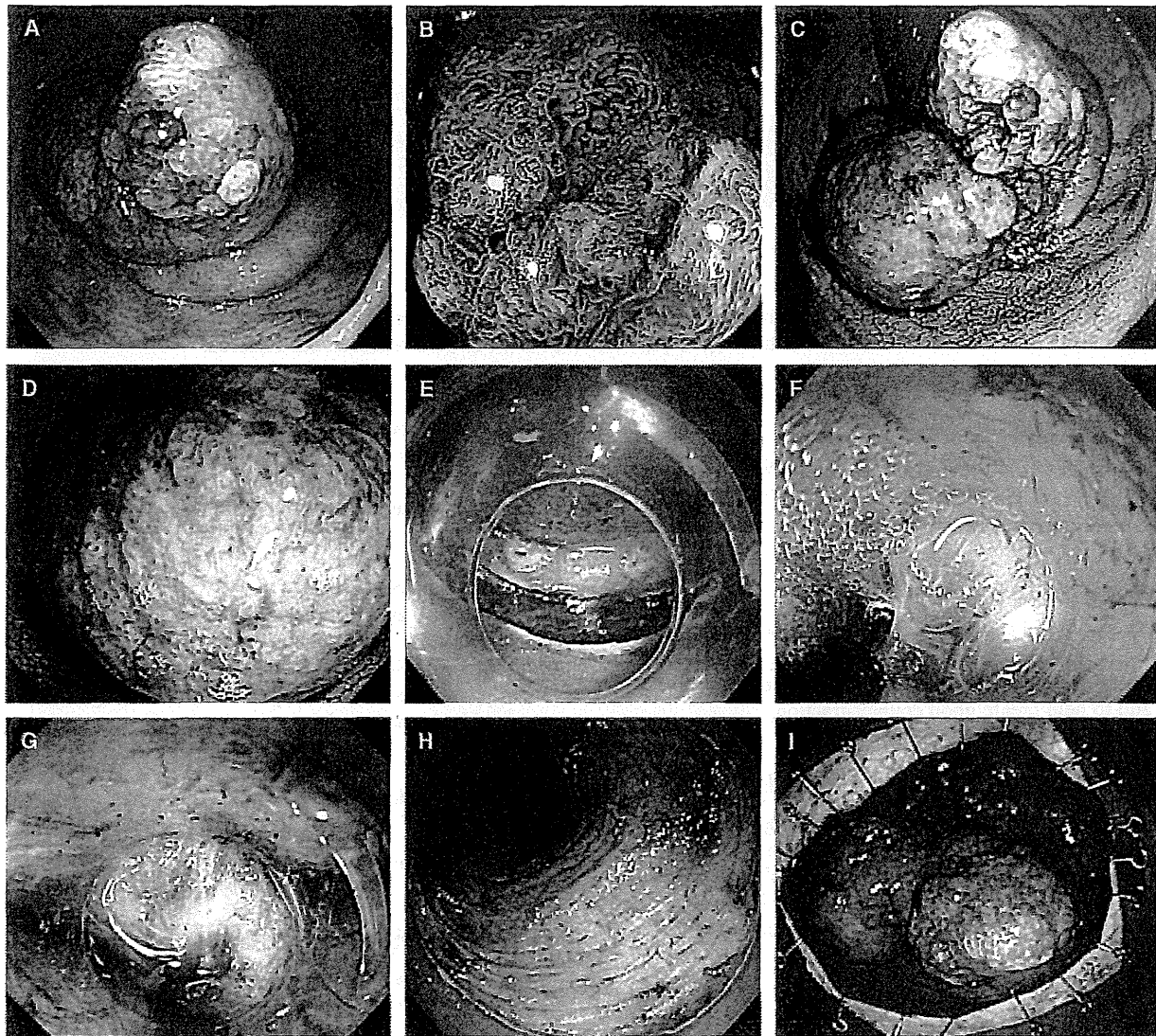


Figure 1 (a) Large Is+Ila (laterally spreading tumor granular-type: LST-G) lesion located in the lower rectum. Estimated size of this tumor was 70 mm in diameter. (b) Narrow band imaging with magnification revealed Sano's type IIIA capillary pattern on the large nodule, suggesting intramucosal cancer. (c) After 0.4% indigocarmine dye spraying, the margin of this LST became apparent and there was no depressed area. (d) Indigocarmine with magnification suggests type VI pit pattern, but this remained unclear because of persistent mucus that could not be removed despite use of proteinase. (e) After injecting Glycerol[®] (Chugai Pharmaceutical Co., Tokyo, Japan) and MucoUp[®] (Seikagaku Co., Tokyo, Japan) into the submucosal layer, marginal resection was started using a bipolar-type knife (B-knife) at the oral side of this lesion using retroflexion of the scope. (f) Submucosal dissection was conducted using an insulation-tipped (IT) knife nano. (g) Severe fibrosis was observed during endoscopic submucosal dissection (ESD) under the large nodule, so careful submucosal dissection was necessary using the B-knife. (h) Ulcer bed after successful en-bloc resection without any complications. (i) Resected specimen measured 70 × 65 mm in diameter.

Scissor-type^{16,29} and tongue-type electro-surgical knives have recently been reported as being easier and safer to use.

The newly developed insulation-tipped electro-surgical knife (IT knife nano, KD-612Q; Olympus Optical

Co., Tokyo, Japan)¹⁵ has a smaller insulation tip than the previous one and the short blade is designed as a small disk to reduce the burning effect on the muscle layer.

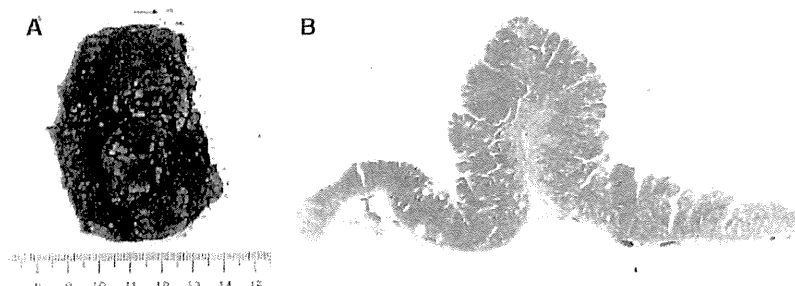


Figure 2 (a) Resected specimen shown in Fig. 1(i) measured 70 × 65 mm in diameter. (b) Histopathological diagnosis was well-differentiated adenocarcinoma with villous tumor, pM, ly0, v0, LM (-), VM (-). Curative resection was achieved.

Hemostatic forceps

Hemostat-Y (H-S2518; Pentax) is a bipolar-type hemostatic forceps and Coagrasper is a monopolar-type forceps (FD-410LR; Olympus Medical Systems Co., Tokyo, Japan).

Distal attachments

Various distal attachments such as ST hood short-type (DH-28GR and 29CR; Fujifilm Medical Co., Tokyo, Japan) are useful for colorectal ESD to slip into the narrow SM layer and to help create good counter-traction.

Other counter-traction methods

Several traction methods have been proposed to facilitate submucosal dissection, such as sinker-assisted ESD,³⁰ thin endoscope-assisted (TEA)-ESD,³¹ S-O clip for traction,^{32,33} cross-counter technique³⁴ and clip with line method.³⁵ All these traction methods enable safer and more effective colorectal ESD.

Carbon dioxide regulator

Carbon dioxide (CO₂) insufflation is necessary to reduce patient abdominal discomfort during the ESD procedure.^{36,37} A CO₂ regulator is available from Olympus (UCR; Olympus Medical Systems) and Fujifilm (GW-1; Fujifilm Medical).^{12,36}

Submucosal injection agents

Submucosal injection solutions are used to lift lesions when carrying out ESD. The time-consuming nature of ESD requires a longer-lasting elevation to provide direct visualization of the cutting line during dissection of the submucosal layer.

Japanese endoscopists generally use Glycerol[®] (Chugai Pharmaceutical Co., Tokyo, Japan)³⁸ for injection into the submucosal layer for colorectal ESD. This consists of 10%

glycerol and 5% fructose in normal saline solution,³⁸ along with a small amount of indigocarmine dye and MucoUp[®] (Seikagaku Co., Tokyo, Japan) which is composed of sodium hyaluronate solution.^{9,10} The use of these agents has resulted in safer, easier and more effective ESD than using regular saline.

During the ESD procedure, a small amount of Glycerol[®]³⁸ (10% glycerin and 5% fructose) is first injected into the SM layer to confirm the appropriate SM layer elevation and then MucoUp[®]^{9,10} is injected into the properly elevated SM layer. Finally, a small amount of Glycerol[®] is injected again to flush any residual amount of the second solution.

Electrosurgical generators

Electrosurgical generators used are VIO300D (ERBE, Tübingen, Germany) or ESG100 (Olympus Medical Co.).

Estimating depth of invasion

All candidate lesions for ESD must be confirmed as being an intramucosal tumor using magnification colonoscopy^{39,40} or endoscopic ultrasonography (EUS) before carrying out the procedure. Biopsies are not recommended before ESD because they can cause fibrosis and may interfere with SM lifting.

RESULTS OF ESD

Outcomes of colorectal ESD in the literature

OUTCOMES OF COLORECTAL ESD have been described by Tanaka *et al.*⁴¹ The en-bloc resection and histological R0 resection rates were 90.5% (61–98.2%, 2740/3028) and 76.9% (58–95.6%, 1385/1801), respectively. Perforation and postoperative bleeding occurred in 5.4% (1.3–20.4%, 180/3339) and 1.8% (0.5–9.5%, 42/2300), respectively. Local tumor recurrence was reported as 1.9% (0–11%, 20/1036) of all ESD cases.

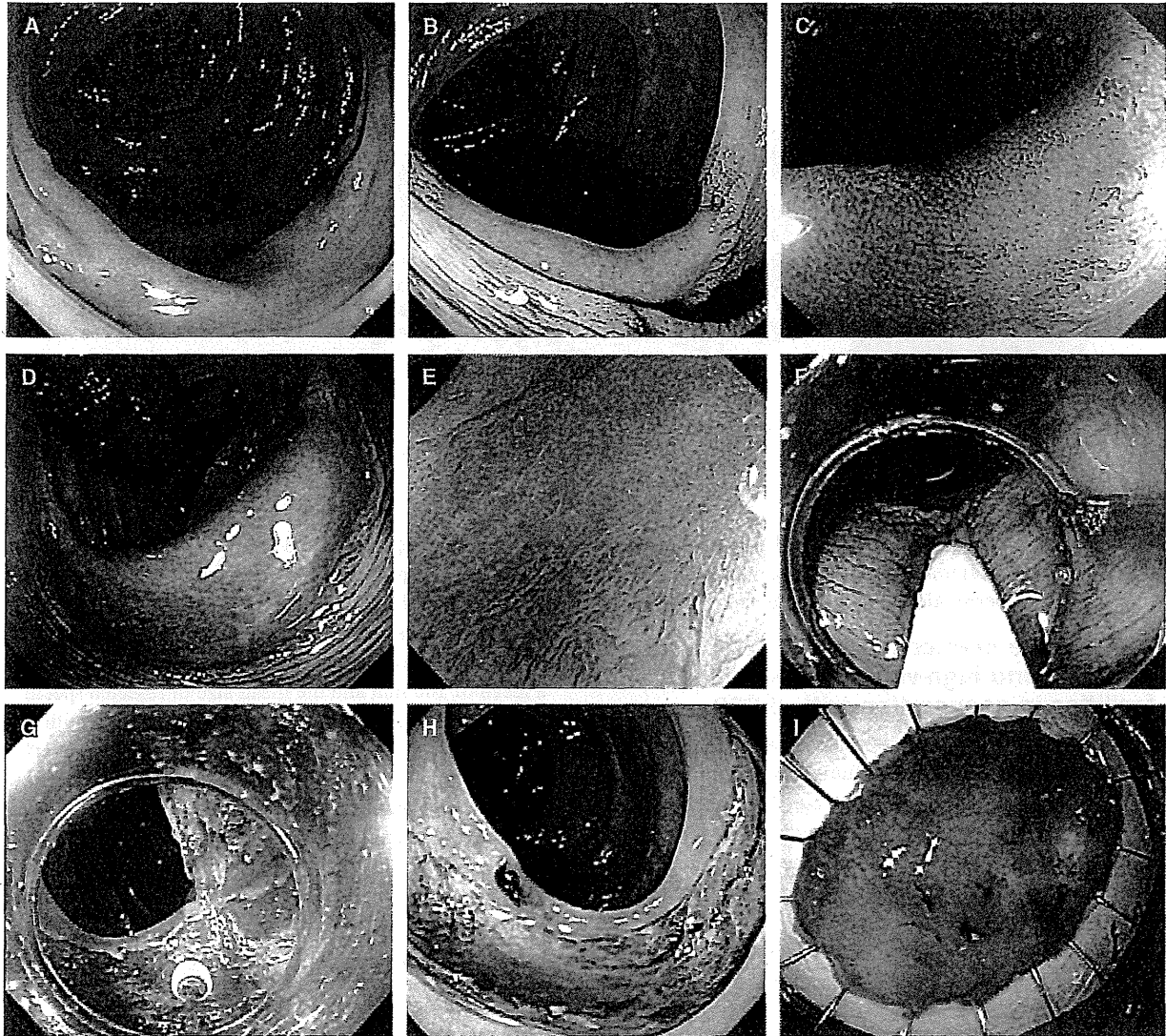


Figure 3 (a) Large O-IIC (laterally spreading tumor non-granular-type: LST-NG) lesion located in the ascending colon. Estimated size of this tumor was 40 mm in diameter. (b) After 0.4% indigocarmine dye spraying, the margin of this LST-NG became apparent. (c) Narrow-band imaging with magnification revealed Sano's type II or IIIA capillary pattern, suggesting intramucosal cancer. (d) Retroflex view of this LST-NG after crystal violet staining. (e) Crystal violet staining with magnification revealed type IIIs and VI (non-invasive) pit pattern, suggesting intramucosal cancer. (f) Submucosal injection of Glycerol® (Chugai Pharmaceutical Co., Tokyo, Japan) and MucoUp® (Seikagaku Co., Tokyo, Japan) into the submucosal layer. (g) After injecting Glycerol and MucoUp into the submucosal layer, submucosal dissection was conducted using an insulation-tipped (IT) knife nano with retroflexion of the scope. (h) Ulcer bed after successful en-bloc resection without any complications. (i) Resected specimen measured 40 × 25 mm in diameter.

Prospective, multicenter study of 1111 colorectal ESD

We reported the results of 1111 colorectal ESD in 1090 patients carried out at 10 specialized institutions in a study conducted from June 1998 to February 2008.⁴² In summary, the en-bloc and curative resection rates were 88% and 89%,

respectively. The mean procedure time was 116 min with a mean tumor size of 35 mm. Perforations occurred in 4.9% with 0.4% delayed perforation and 1.5% postoperative bleeding.

In this previously reported multicenter study, multivariate analysis revealed that a large tumor with size ≥ 50 mm and a

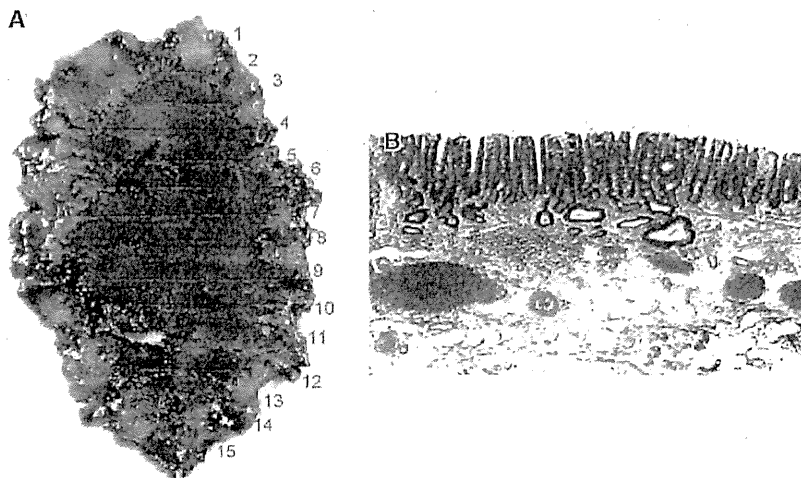


Figure 4 (a) Resected specimen shown in Fig. 1(i) measured 40 × 25 mm in diameter. (b) Histopathological diagnosis was well-differentiated adenocarcinoma, pSM (100 μm), ly0, v0, LM (-), VM (-). Curative resection was achieved. Histologically, multifocal superficial submucosal (SM) invasions were diagnosed as indicated by red lines (Fig. 4a). These multifocal SM invasions were impossible to predict before the treatment, despite using magnified colonoscopy.

lower experience level (<50 ESD carried out) were independent factors for a significantly increased risk of complications including perforation and delayed bleeding.⁴²

Prospective multicenter study at 18 medium- and high-volume specialized facilities in cooperation with JSCCR

To evaluate the current situation in Japan regarding endoscopic treatment of colorectal tumors measuring ≥ 20 mm, the Japan Society for Cancer of the Colon and Rectum (JSCCR) conducted a prospective multicenter study at 18 medium-volume and high-volume specialized facilities.⁴³ From October 2007 to December 2010, 1029 conventional EMR and 816 ESD were carried out. The average ESD procedure time was 129 min in the ≥ 40 mm group compared to 79 min in the 30–39 mm group and 66 min in the 20–29 mm group. As lesion size increased, the en-bloc resection rate decreased significantly in the EMR group (trend $P < 0.01$), but remained $>93\%$ in the ESD group. Perforation and delayed bleeding of EMR/ESD were 0.8%/1.6% ($P < 0.05$) and 2%/2.2% ($P = 0.3$), respectively.

Taking this paper into consideration, even though ESD for larger lesions had a higher perforation rate compared to EMR, the higher en-bloc resection rate of ESD would justify the risk of complications. In addition, recent development of ESD devices and technical progress may decrease the complication rate in the near future. A 6-month or 1-year follow up was done in every EMR/ESD case and the study results will be published shortly.

Recent clinical outcomes of ESD at NCCH

From a total of 900 ESD, the en-bloc resection rate was 91% and the curative resection rate was 87%. There were a total of

687 (76%) carcinomas and the remaining 213 cases were mostly adenomas. Among carcinomas, 117 cases (17%) were diagnosed as SM deep and/or lymphovascular invasion and additional surgery was recommended for most of these non-curative cases. Median procedure time was 60 min with a mean of 100 min and the mean size of resected specimens was 40 mm (range, 20–150 mm). Postoperative bleeding rate for colorectal ESD was 1.7% (15/900) whereas the perforation rate was 2.7% (24/900). Only one immediate and one delayed perforation required emergency surgery.

Considering our data, perforations after ESD have dramatically decreased (from 5% in 2007¹¹ to 1.9%¹⁸ in recent years) by the recent development of ESD devices and the establishment of ESD as a therapeutic strategy.

Comparisons between ESD and EMR

The primary advantage of ESD compared to EMR⁴⁴ is a higher en-bloc resection rate for large colonic tumors that would have been treated by surgery before the development of the ESD technique. Consequently, ESD has a lower recurrence rate compared to EMR (2% vs 14%)⁴⁴ and also provides a better quality of life for patients compared with surgery. Further studies^{13,16,17} have also reported similar advantages of ESD compared with conventional EMR.

In the past, piecemeal EMR had been considered a feasible treatment for colorectal LST because of a low local recurrence rate for such tumors and repeated endoscopic resection was considered sufficient for most local recurrent tumors in Japan.⁴⁵ In Western countries, piecemeal EMR is still the gold standard treatment for LST >20 mm in diameter because of the technical difficulty and longer procedure time of ESD.²² In our case series,⁴⁴ piecemeal EMR was also effective in treating many LST-G ≥ 20 mm and the

perforation rate was lower than ESD (N.S.), but three cases (1.3%) required surgery after such piecemeal resections including two cases of invasive cancer recurrence. A third piecemeal resection also required surgery because of technical difficulty in carrying out another EMR after recurrence of intramucosal cancer. Other groups,^{21,22} however, have reported a lower incidence of SM invasion in LST-G and no invasive recurrence after piecemeal EMR. However, there may be some bias in these reports, including small sample size and limited long-term follow up.

Our results make a case for ESD or laparoscopic assisted colectomy (LAC) surgery for LST-G >30 mm in size due to the increased risk of SM invasion and to improve histological assessment of these lesions. However, further data are urgently required to recommend a widespread change in clinical practice.⁴⁴ Future studies should be designed to compare the clinical outcomes between ESD and surgery rather than between ESD and EMR, because the indications for ESD and EMR are different, as are the relevant tumor characteristics.

ESD and surgery

In addition to ESD, laparoscopic assisted colectomy (LAC) is another minimally invasive alternative to open surgery for colorectal cancers. Currently, there is a lack of comparative effectiveness data on ESD versus LAC resection for early colorectal cancer. This information would be most enlightening given the considerable differences in the potential benefits and risks between the two procedures.

At NCCCH, we retrospectively compared ESD with LAC as minimally invasive treatments for early colorectal cancer.⁴⁶ This single-center retrospective comparison indicated that ESD was safe and provided an excellent prognosis despite different indications for ESD and LAC (ESD for non-invasive tumors vs LAC for invasive cancers with risk of LNM). The indications for ESD and LAC are quite different. However, if the primary indication is a non-invasive colorectal lesion diagnosed preoperatively as intramucosal to SM1 (<1000 μ m), the patient's quality of life following treatment would likely be better with ESD.⁴⁶

Although there have been some cases requiring additional surgical resection after endoscopic resection for SM invasive cancer, colorectal ESD has succeeded in reducing the need for surgery for mucosal carcinomas and has improved the overall quality of life for most patients.⁴⁷

ESD and trans-anal endoscopic microsurgery or trans-anal resection

Various minimally invasive local excision treatments for early rectal cancer, such as trans-anal resection (TAR), trans-anal endoscopic microsurgery (TEM), and endoscopic resec-

tion techniques, including EMR and ESD, are gaining acceptance worldwide. For rectal cancer treatment, however, a longer procedure time is required for LAC, and TAR and TEM are more invasive than ESD with a significantly higher recurrence rate.^{48,49} Accordingly, ESD is the preferred choice for early rectal cancers (Fig. 1).

ESD outside Japan

From a technical perspective, colorectal ESD has become increasingly standardized at specialized referral centers not only in Japan, but also outside Japan, including Asia and Western countries.^{49–56} In our previous questionnaire survey¹⁸ that included two Asian institutions outside Japan, quite surprisingly, 250 colorectal ESD were done recently in Chinese institutions during a 1-year period.

Long-term outcomes of colorectal ESD

Detailed long-term outcomes of colorectal ESD are yet to be defined. Niimi *et al.*⁵⁷ reported that the 3- and 5-year overall/disease-specific survival was 97.1/100% and 95.3/100%, respectively, during a median follow up of 38.7 months (range 12.8–104.2) among 310 consecutive colorectal epithelial neoplasms (146 adenomas, 164 carcinomas), in 290 patients. Short-term outcomes for colorectal ESD are well known, as they have been reported by several institutions.⁵⁸ However, detailed long-term outcomes in colorectal ESD remain unclear. We therefore need to continue to collect more information on long-term outcomes in order to confirm the feasibility of colorectal ESD.

DISCUSSION

UNLIKE GASTRIC OR esophageal cancers, most colorectal neoplasms, such as LST-G, are believed to develop from an adenoma-carcinoma sequence. Thus, some LST-G lesions are thought to be effectively treated by piecemeal EMR. However, it is essential to avoid resecting the cancerous area of the LST lesion in a piecemeal fashion when carrying out EMR. Resecting the entire lesion also enables a correct histological diagnosis and determination of whether endoscopic follow up is sufficient or whether additional treatment is required.

Non-polypoid-growth (NPG)-type tumors, such as LST-NG lesions and 0-IIc lesions, have a higher rate of SM1 invasion. This can be difficult to predict endoscopically even using magnification. Therefore, these lesions should be treated by en-bloc resection rather than by piecemeal EMR based on our previous clinicopathological analyses of LST.^{4,19} Furthermore, these non-polypoid type tumors are known to be difficult to detect even using high-definition

colonoscopy. Endoscopists should understand the existence and importance of NPG-type tumors.

LST-G >30 mm^{4,19} and intramucosal tumors with non-lifting sign are technically difficult to resect en-bloc using conventional EMR. Most of these lesions with a non-V pit pattern are considered oncologically not so malignant when compared with a NPG-type tumor. We should therefore consider the endoscopist's skill level, complication rate and the procedure time when selecting ESD for these lesions.

CONCLUSION

ENDOSCOPIC SUBMUCOSAL DISSECTION is a safe and effective procedure to treat colorectal LST-NG >20 mm and 0-IIc lesions >20 mm. Both of these types of lesion are difficult to resect en bloc using conventional EMR. LST-G >30 mm, intramucosal tumors with non-lifting sign and large sessile lesions are possible candidates for ESD if carried out by an expert. ESD has great advantages compared to EMR in providing a higher en-bloc resection rate as well as being less invasive than surgery. Further development and refinement of ESD-related instruments, devices, equipment and injection solutions will help facilitate the increasing use of colorectal ESD throughout the world.

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CONFLICTS OF INTEREST

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