Endoscopic submucosal dissection for colorectal neoplasms

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Abstract

Although endoscopic submucosal dissection (ESD) gains acceptance as one of the standard treatments for esophageal and stomach neoplasms in Japan, it is still in the developing stage for colorectal neoplasms. In terms of indications, little likelihood of nodal metastasis and technical resectability are principally considered. Some of intramucosal neoplasms, carcinomas with minute submucosal invasion, and carcinoid tumors, which are technically unresectable by conventional endoscopic treatments, may become good candidates for ESD, considering substantial risks and obtained benefits. ESD as a staging measure to obtain histological information of the invasion depth and lymphovascular infiltration is acceptable because preoperative prediction is difficult in some cases. In terms of techniques, advantages of ESD in comparison with other endoscopic treatments are to be controllable in size and shape, and to be resectable even in large and fibrotic neoplasms. The disadvantages may be longer procedure time, heavier bleeding, and higher possibility of perforation. However, owing to refinement of the techniques, invention of devices, and the learning curve, acceptable technical safety has been achieved. Colorectal ESD is very promising and become one of the standard treatments for colorectal neoplasms in the near future.

Key words: Colorectal neoplasm; Early colorectal cancer; Endoscopic submucosal dissection; Endoscopic mucosal resection; Endoluminal surgery

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INTRODUCTION

Endoscopic submucosal dissection (ESD), which first developed in the stomach, is a new endoluminal therapeutic technique involving the use of cutting devices to permit a larger resection of the tissue over the muscularis propria[1]. The technique has also spread to other organs in the gastrointestinal tract[2].

In comparison with endoscopic mucosal resection (EMR), ESD needs very experienced hands because of its far more complex procedural sequence. However, the obtained outcomes seem to be more advantageous especially for early-stage neoplasms with a large size or submucosal fibrosis, although long-term data are still lacking. Additionally, by using ESD technique, the resected area can be precisely controlled by the operators, which may not only lead to complete removal of even large lesions, but also to the least non-neoplastic mucosal resection. In this review, the present indications, techniques, and outcomes of colorectal ESD were described including our experiences for further development of this wonderful technique.

INDICATIONS

Two aspects are considered to determine the application...
of ESD for each lesion by each operator. The first is a little likelihood of lymph node metastasis and the second is the technical resectability. The former has been determined by the large numbers of surgically resected cases in each organ before establishment of ESD and the latter may be determined by the applied technique, the expertise of the operators, the location of the lesions or their characteristics.

**Aspects of nodal metastasis**

From the large numbers of surgically resected colorectal cases, intramucosal carcinomas and those with slight submucosal invasion (<1000 micrometers below the muscularis mucosa; sm1) without lymphovascular infiltration have little risk of nodal metastasis.

Tumor morphology and surface pit pattern are good endoscopic indicators for submucosal invasion. From this aspect, depressed lesions, laterally spreading tumors of non-granular type (LST-NG) and large protruding tumors are considered as good candidates for ESD because these lesions have a high risk of submucosal invasion, which may be difficult to diagnose preoperatively, and a thorough histopathological assessment of the resected specimen is essential. It is controversial whether one should perform ESD or piecemeal EMR for laterally spreading tumors of granular type (LST-G), because most lesions are intramucosal and the endoscopic prediction of invasiveness is highly feasible. To obtain the above information, magnification chromoendoscopy or narrow band imaging endoscopy is very useful.

**Technical aspects**

In terms of technical resectability, en bloc resection is more desirable than piecemeal resection for accurate assessment of the appropriateness of the therapy, because the depth of invasion and lymphovascular infiltration of cancer cells (that are considerable risk factors for nodal metastasis) are not accurately assessed by piecemeal resection. Almost all possible node-negative lesions can be resected en bloc by ESD, when very experienced hands treat them. This does not mean that all endoscopic resection should be performed as ESD. Polypectomy or EMR is beneficial for patients with pedunculated neoplasms or small neoplasms because of the little invasiveness. If the lesions are apparently premalignant neoplasms, piecemeal resection by using EMR may be permissible with the best balance of risks and benefits. Surgical organ resection with lymphadenectomy should be applied to those neoplasms with high probability of positive lymph nodes or failure in complete removal by ESD. Recurrent lesions can be also indicated for ESD, if they fulfill the criteria of no nodal metastasis, but indication should be carefully determined considering the risks of accompanying complications.

Even for lesions that meet the node-negative criteria, laparoscopic or open surgery may be selected in some institutions considering the location and size of the lesion. The rectum is fixed to the pelvis, therefore the endoscope is more easily maneuvered than in other locations of colorectum. Furthermore, panperitonitis may be less likely, even if the muscularis propria is torn, although penetration leads to air accumulation in the retroperitoneal space, which may then spread to a wider area. On the other hand, there are several tortuous folds in the colon. Peristalsis and residual feces may sometimes disturb ESD procedure. So it is commonly believed that the technical difficulty of colon ESD exceeds those of the stomach, the esophagus, and the rectum, although there are many differences.

**Carcinoid**

Carcinoids are classified based on organ site and cell of origin and occur most frequently in the gastrointestinal tract (67%) where they are most common in small intestine (25%), appendix (12%), and rectum (14%). In the colorectum, those in the appendix should be treated by laparotomy considering risks and benefits. Rectal carcinoids < 2 cm in size may become candidates of ESD, because those rarely metastasize, although another group revealed that colorectal carcinoids < 1 cm without lymphovascular infiltration could be curatively treated by local resection, but others would need radical nodal dissection.

However, almost all lesions less than 1 cm in size are treatable by using band ligation resection or cap-technique and the application of ESD for carcinoids may be limited. When the lesions are in intermediate size, such as 1-2 cm, or invade massively the submucosal layer, which may result in tumor-positive margin resection, ESD should be applied.

**TECHNIQUES**

The operation is performed in in-patients setting. The day before ESD, the patients eat only low fiber diet and 10 mL of 0.75% sodium picosulfate solution is prescribed before bed. In the early morning of the operation, 10 mg of mosapride citrate and 2 L of an isotonic polyethylene glycol electrolyte solution are used for bowel preparation.

The techniques of ESD are slightly different according to the individual operators at different hospitals, although main procedural sequence is quite similar. In our hospital, the ESD is recently carried out using a slim, single-channel, and high-definition endoscope with the water-jet system (e.g. GIF-Q260J, PCF-Q260J, Olympus; EG-2990i, EC-3890i, HOYA Pentax) and a high-frequency generator with special cutting (ENDOCUT mode) and coagulation (swift coagulation mode) current (VIO 300D, ERBE Elektromedizin GmbH, Tübingen, Germany). If the lesion is located within the distance where upper gastrointestinal (GI) endoscopes can reach, application of these upper-GI endoscopes is also preferable to using a slim colonoscope, because they have greater maneuverability. The transparent attachment is fitted on the tip of the endoscope mainly to obtain a constant

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October 15, 2009 | Volume 1 | Issue 1 |
endoscopic view and to create tension on the connective tissue for the submucosal dissection. The representative procedural sequence is shown in the Figure 1.

**Marking around the lesions**
Markings are not made because the margins of the lesions are clearly identified and the colorectal wall is thin enough to perforate only by marking.

**Creating a submucosal fluid cushion**
The solution is colored in slight blue with mixture of a small amount of indigocarmine. The first injection, about 1 mL in volume, to create an initial bulge where the first mucosal incision should be made should be done with normal saline in order to place hyaluronic acid in the appropriate submucosal layer. After confirming the right needle depth, additional injection by using hyaluronic acid is followed. The volume of injection is about 2 mL at one time, and injection is repeated several times before starting mucosal incision, until the targeted area is lifted enough. It is important to count the volume of injection loudly every 0.2 mL so that the operator can determine whether the injection is working effectively. Complete marginal cutting of the mucosa before submucosal dissection is not necessary; mucosal incision and submucosal dissection are repeated several times before marginal cutting is complete. After exposure of the submucosal layer, additional submucosal injection is needed to lift up the layer you intend to cut. The total injection volume to complete ESD is from 20 mL to 60 mL according to the lesion size.

**Incising the mucosa outside the lesion**
After the lesions are lifted, a mucosal incision is made with a flex-knife or a splash-needle (Figure 2). The knife is fixed at a length of 2 mm and gently pressed onto the mucosa to produce a cutting effect using the ENDOCUT I mode (effect 1 duration 3 interval 3) for a flex-knife or the ENDOCUT Q mode (effect 3 duration 1 interval 3) for a splash-needle. The distal half of the mucosal incision is completed first, followed by the proximal half. If the mucosal incision reaches below the muscularis mucosa, the submucosal layer dyed blue by the injected

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**Figure 1** Colorectal endoscopic submucosal dissection. A: Chromoendoscopy; B: Submucosal injection; C: Mucosal incision; D: Submucosal dissection; E: Mucosal defect; F: Resected specimen.

**Figure 2** Electrosurgical knife. A: Flex-knife; B: Splash-needle; C: Hook-knife.
fluid comes into sight. If the blue submucosal layer does not appear, it means that the muscularis mucosa has been cut incompletely. In this situation, the incising line is traced again until the blue submucosal layer comes out. The starting point for cutting depends on the location of the lesions. Principally, it is recommended to start cutting distally from the endoscope. Retroflex positioning of the endoscope is usually used, if possible, in the cutting of a distal part, but cutting is also done in the straight position when retroflex positioning being impossible. As the submucosal injection solution retained in the submucosa comes down toward the ground, it is better to start cutting from an opposite part of the ground as well as a distal part or put the lesion on an opposite part of the ground if the patient’s body positions are changeable.

Dissecting the submucosal layer beneath the lesion
Small lesions can be resected with an electrosurgical snare only after circumferential mucosal incision without submucosal dissection. However, large lesions, lesions with submucosal fibrosis, or lesions located in a tortuous area cannot be resected by an electrosurgical snare, which means dissecting the submucosa completely. Dissection of the submucosa is begun from the proximal area to the distal end. The principle knife used for the submucosal dissection is the same length as that used for the mucosal incision using swift coagulation mode (effect 4, output 40W) for a flex-knife or forced coagulation mode (effect 3 output 30W) for a splash-needle, and in difficult dissections the hook-knife in swift coagulation mode (effect 4, output 40W) is also used in combination with the principle knife. To control bleeding, a pair of hemostatic forceps (SDB2422, HOYA Pentax) is used in soft coagulation mode (effect 5, output 50W). The device has a narrow opening angle, a small cup, and a blunt edge, which looks similar to a pair of small-sized hot-biopsy forceps. After pinpoint holding and mechanical compression, electrocoagulation is easily performed to obtain hemostasis. The water-jet system supplies a continuous jet of water at high pressure, which easily and swiftly washes away any blood obstructing the visual field, allowing identification of the vessel that is bleeding. Gravity is used for submucosal dissection by changing the patient’s body positions (Figure 3). The lesions should be positioned opposite to the ground because the detached parts of the specimen come down and the connective tissue in the submucosa to be dissected is stretched enough to enable an easy and safe dissection. The injected solution in the submucosa leaks out gradually after mucosal incision, and the submucosal cushion flattens down with time. Thus, it is important to start dissecting the submucosa immediately from the incising part of the mucosa before marginal mucosal cutting.

Management after endoscopic submucosal dissection
After resection of the lesion, visible vessels of the resulting artificial ulcer are also treated with the hemostatic forceps to prevent delayed bleeding, but it is also kept in mind that the intensive coagulation of visible vessels on the exposed muscle layer may cause delayed perforation. So it is advisable to use hemoclips to treat these vessels. Three hours after the ESD, patients are permitted to drink a small amount of water with bed rest. The next day, if the patient’s symptoms, laboratory findings, and chest X-ray are unremarkable, a light meal and walking is permitted and the patients are discharged within 1 wk. If complications occur, the schedules are changed according to the individual patient’s conditions.

OUTCOMES
In comparison with outcomes of other endoscopic treatments, those of ESD are extremely good and promising as shown in the Table [15,20,24-31]. The en bloc resection rate is around 90% even if the mean tumor size is more than 20 mm. Although the en bloc + R0 (tumor free margins) resection rate is lower, the marginal cutting around the lesions before submucosal dissection results in extremely lower rates of local recurrence. Longer operation time (mean 61-110 min) and complications may become disadvantages. Perforation is a major complication related to ESD, which is experienced in around 5% of cases. Immediately recognized perforation can be successfully sealed with endoclips and conservatively observed without emergency laparotomy by antibiotics and no feeding for a few days in almost all cases. However, in some cases of perforation, especially delayed perforation, emergency laparotomy is necessary. Bleeding is the most common complication in the stomach, but in case of colorectum, the complication occurs less frequently and is typically minor and treatable with colonoscopy.
FUTURE PERSPECTIVES

Because of the remarkable progress in the endoscopic technologies, ESD is applicable in the colorectum with promising results as well as the stomach[33] and the esophagus[34]. However, there is still a room for innovation. Our major concerns are (i) expansion of indications owing to novel knowledge for node-negative cancer, (ii) technical innovation for quicker and safer techniques, and (iii) training system to spread the technique.

In terms of indications, the criteria of node-negative cancer are only obtained by histological evaluation with hematoxylin & eosin staining of surgically-resected materials so far, which revealed that depth of cancer invasion and lymphovascular infiltration of cancer cells are major determinants of nodal metastasis. However, we have to notice that the incidence of nodal metastasis from submucosal invasive cancers is at most 10%[35], which means that the rest of cases might be cured by local treatment including ESD. In the near future, we expect that unnecessary laparotomy will be avoidable, by using novel predictive markers of nodal metastasis, for example, using gene analysis of biopsy samples or resected specimens by ESD. Furthermore, combination with chemo-/radio-therapy may achieve less invasive treatments instead of colectomy or rectal resection with lymph node dissection.

In terms of technical aspects, major drawbacks of ESD may be the long procedure time and its complexity, and then, that the obtained results are highly operator-dependent so far. Except for the rectum, tortuous structure and the peristalsis prevent from constant endoscopic view field and stability of the endoscope. So, the innovation regarding electrosurgical knives and submucosal fluid cushion is insufficient.
to achieve the goal and we look forward to a big breakthrough regarding novel instruments or endoscopes, which enable us to perform precise cutting easily and quickly without complications.

Until the above dream comes true, it is absolutely necessary to establish the training system to spread the present technique. Because ESD in the colon is far more difficult than that in the stomach, step-by-step approach, e.g. as shown in the Figure 4, which is performed in our university, is recommended. Among locations in the colorectum, it is preferable to start ESD from the rectum. The endoscopists who graduate from the fifth step can become experts and trainers for the next generation in our university.

In summary, colorectal ESD has already been established with favorable outcomes in the advanced institutions. We are convinced that colorectal ESD will become one of the standard treatments for early-stage colorectal neoplasms not only in Japan but also all over the world in the near future.

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