Endoscopic resection of early gastric cancer is a well-established standard therapy in Japan, and is increasingly used in other countries. The development of endoscopic submucosal dissection (ESD) for early gastric cancer provides en bloc R0 specimen, regardless of size and/or location. On the other hand, for many years, conventional endoscopic mucosal resection and surgery were the only available treatments for large colorectal tumors, including laterally spreading tumors. Recently, ESD has also been increasingly applied to the colon and rectum. However, ESD has not yet been fully established as a standard therapeutic procedure for early colorectal carcinoma in Japan.6–10 National health insurance covers the expense of ESD, as a therapeutic procedure, for early gastric and esophageal carcinoma. However, ESD has not yet been recognized as a standard therapeutic procedure for colorectal lesions because of its technical difficulty and complications, such as perforation and longer procedure time than the conventional endoscopic mucosal resection. In this report, we provide an overview of the indications for colorectal ESD and presented clinical outcome, regarding the safety and efficacy in our hospital with a review of the published works.

Keywords: Early colorectal cancer, Endoscopic submucosal dissection, Lower gastrointestinal tract

Introduction

Endoscopic submucosal dissection (ESD) was initially developed for the treatment of early gastric cancer to facilitate en bloc resection of large superficial tumors.1–5 The primary purpose of ESD is to decrease the risk of local cancer recurrence, by performing en bloc resection and providing an accurate histopathological diagnosis. ESD is widely used for the treatment of carcinoma of the early gastric and esophageal carcinoma in Japan.6–10 National health insurance covers the expense of ESD, as a therapeutic procedure, for early gastric and esophageal carcinoma. However, ESD has not yet been recognized as a standard therapeutic procedure for early colorectal carcinoma because of its technical difficulty with the risk of complications, such as perforation and bleeding and its longer procedure time. More recently, with the development of various new instruments,11–15 the increased effectiveness of colorectal ESD has been reported.16–25 The number of medical facilities that perform colorectal ESD has also been increasing recently in the West.26–28

This review focuses on the process of development of the upper gastrointestinal (GI) ESD, an indication for lower GI ESD, and several differences between Japan and Western countries in performing ESD for the lower GI lesions.

History of endoscopic treatment for GI tumors

Endoscopic resection to treat cancer is perhaps the most gratifying endoscopic procedure to perform because of its minimal invasiveness and curative potential. Endoscopic resection of early gastric cancer (EGC) is a standard therapeutic choice in Japan and is increasingly used globally.29,30 Endoscopic resection offers minimally invasive treatment at a lower cost, but with comparable efficacy to surgery. It allows complete pathological staging of the cancer, which is critical for risk stratification of metastatic potential.31 Patients who are stratified to have no or lower risk for developing lymph node metastasis than the risk of mortality from surgery are ideal candidates for endoscopic resection.32

The first endoscopic resection of early cancer was reported in colorectal polyectomy, using high-frequency electric surgical unit.33 Indeed, the first endoscopic polypectomy used to treat pedunculated or semipedunculated EGC was first described in Japan, during the year 1974. The “strip biopsy” technique, an early method of endoscopic mucosal resection (EMR) technique, was devised in 1984 as an application of endoscopic snare polypectomy.34 For this method, a double channel endoscope is used in order to snare the early cancer while it is being pulled toward the endoscope with a grasper. The technique was designed for resection of small lesions with a surrounding normal margin, thus allowing a proper pathological assessment. To ensure that the snare captures the entire lesion with a 5-mm surrounding normal margin, in 1988, a technique called ERHSE (endoscopic resection with local injection of hypertonic saline epinephrine solution) was developed by Hirao and colleagues.35 The technique is composed of performing a snare resection of a cancer with a normal margin,35 which has been isolated with normal surrounding mucosa, by circumferential incision into the
submucosa, thus ensuring en bloc R0 resection. In this technique, after injection of hypertonic saline and diluted epinephrine, the periphery of the lesion was incised using a needle knife, and the lesion was removed using a snare. Unfortunately, this rather amazing technique required considerable skills to perform given the risks of perforation from using the needle knife.

EMR with cap-fitted panendoscope method (EMRC) was developed in 1992 for the resection of early esophageal cancer and directly applicable for the resection of EGC.30 The technique uses a transparent plastic cap, which is mounted to the tip of a standard endoscope. A specialized snare is prelooped inside the groove of the inner aspect in the distal part of the cap, thus allowing its use to cut the lesions that are suctioned into the cap. The EMR technique using ligation, which was subsequently extended to EMR using multiband ligation (EMR-L/EMR-MBL), utilizes band ligation to create a “pseudopolyp” by suctioning the lesion into the banding cap and deploying a band underneath it.37,38 The EMR and EMR-L/EMR-MBL technique have the advantage of being relatively simple. These techniques require the use of a standard endoscope, without any additional equipment or assistant. However, these techniques cannot be used to remove the lesions en bloc larger than 2 cm.39,40 Piecemeal resections in lesions larger than 2 cm leads to a high risk of local cancer recurrence and inadequate pathological staging.41 Therefore, methods to remove large lesions en bloc were developed.42

Development of ESD for EGC

The Insulated-tip diathermic knife (IT-knife) was devised in late 1990s at the National Cancer Center Hospital Japan, in order to resolve the problems observed during the EMR and ERHSE techniques for the resection of EGC. The knife has a ceramic ball tip, thus preventing it from puncturing the wall during the application of cautery and causing perforation. The knife can also be used to dissect the submucosa, which leads to the name of the technique—ESD technique.13,14 Subsequent studies have proven that ESD, using a standard single-channel endoscope, can be used for the resection of large lesions en bloc, allowing for a precise pathological staging.

With the development of ESD, the indication criteria for endoscopic resection were revised. The empirical indications for EMRC were therefore: (1) papillary or tubular (differentiated) adenocarcinoma, (2) less than 2 cm in diameter, (3) without ulceration within tumor, and (4) no lymphatics or vessels involvement.43 Clinical observations have noted that the empirical indications for EMR are too strict and lead to unnecessary surgery. Therefore, expanded criteria for endoscopic resection have been proposed, especially after large en bloc resection could be accomplished using ESD.44,45 Long-term survival and outcomes studies also showed that ESD patients who have the treatment following the expanded criteria are similar to those who have the treatment following the guideline criteria.46 Other ESD knives46–50 and techniques have since been developed and studied in detail. Within less than a decade, ESD has become the standard of treatment for resection of EGC in Japan.

Conventional EMR for lower GI tumors

Recently, ESD has also been increasingly applied to the colon and rectum (Fig. 1A–D). Many studies by Japanese endoscopists have reported that colorectal ESD can overcome the technical limitation of EMR and achieve higher en bloc resection rates16–23 with the development of various new devices.11–14 However, this procedure is known to have several disadvantages compared to conventional colorectal EMR: greater technical difficulty, longer procedure time, and increased risk of complications, including perforation and bleeding.

EMR is indicated for the treatment of superficial, early-stage colorectal cancer because of its minimal invasiveness and excellent results in terms of clinical outcomes.33,44 However, conventional EMR techniques currently used for the resection of laterally spreading tumors (LSTs)48–51 are inadequate for the en bloc resection of flat lesions ≥20 mm because of incomplete removal and problems with local recurrence.52 Conventional EMRs usually resulted in endoscopic piecemeal mucosal resection (EPMR), particularly for large LSTs ≥20 mm with reports of local recurrence rates, ranging from 7.4% to 17%.49,52,53 Most of those recurrences, however, received repeated endoscopic treatment with excellent results in terms of the preservation of the colorectum. But only a few cases required surgery after EPMRs in the long-term follow-up study.54 Those cases may originally have had either submucosal invasion or lymphatic invasion that was not diagnosed histologically because of the increased difficulty in assessing a piecemeal resection.

Indications for lower GI ESD

Colonic LSTs are good candidates for endoscopic treatment, because they extend laterally rather than vertically. Based on clinicopathological analysis of LSTs, LST nongranular type (LST-NG) has a higher rate of submucosal invasion, and diagnosis of tumor depth is more difficult to make endoscopically compared to LST granular type (LST-G).51 LST-G showing adenoma or focal cancer in adenoma is an indication for EPMR under the condition that the cancerous portion is perfectly resected en bloc. Observation of the pit pattern54–56 with a magnifying endoscope is essential before piecemeal EMR. Endoscopic treatment is indicated for the adenoma and intramucosal or submucosal superficial (sm1: less than 1000 μm from the muscularis mucosae) colorectal cancer because of its minimal invasiveness and negligible risk of lymph-node metastasis.57

In our institution, we performed preoperative endoscopy and examined the lesion under magnifying chromoendoscopy for all cases. Then, we diagnosed the depth of the lesion and determined the most appropriate procedure. An invasive pattern was considered a contraindication for ESD.55,56 The existence of a noninvasive pattern, as determined by magnification chromoendoscopy, was the minimum requirement for all lesions that were candidates for ESD and EMR. When a lesion was detected by conventional endoscopic examination, surface mucous was washed away with lukewarm water that contained pronase (Pronase MS; Kaken Pharmaceutical Co., Ltd., Tokyo, Japan), and then 0.4% indigo-carmine dye was sprayed over the lesion to enhance its surface detail. High-magnification colonoscopes (CF-H260AZI, CF-FH260AZI, and PCF-Q260AZI; Olympus Optical Co., Ltd., Tokyo, Japan) were used to evaluate the surface character to differentiate an invasive pattern from a noninvasive pattern. The invasive pattern is characterized by irregular and distorted epithelial crests, observed in a demarcated area, suggesting that sm invasion is >1000 μm, while a noninvasive pattern does not have this finding, which suggests intramucosal neoplasia or sm invasion <1000 μm. When high-magnification observation with indigo-carmine dye was insufficient to determine the surface structure, we performed staining with 0.05% crystal violet. Based on extensive clinicopathological analyses, we defined the indications for ESD.

In our institution, the indications for colorectal ESD are lesion size more than 20 mm for LST-NG or more than 30 mm for LST-G. An LST-G 20–30 mm can be treated by planned EPMR, rather than ESD with the area, including the largest nodule resected first followed by the remaining tumor. Mucosal lesions with
Fig. 1. Endoscopic submucosal dissection for a 30 mm laterally spreading tumor nongranular (LST-NG) type with scar after endoscopic mucosal resection located in the transverse colon. (A-1) Conventional colonoscopy image. (A-2) Conventional colonoscopy image following 0.4% indigo-carmine dye spraying. (B) Magnified view revealing a non-invasive pattern. (C-1) An injection solution was injected into the submucosal layer to lift the lesion. (C-2) Submucosal layer with fibrosis. (C-3) After ESD view. (D-1) Histological image, in the part of black box is submucosal invasion (HE staining). (D-2) Histological diagnosis; well-differentiated adenocarcinoma (tub1), pSM (50 μm), ly0, v0, pHM0, pVM0.
Table 1  Indication of Endoscopic Submucosal Dissection (ESD) for Colorectal Tumor by Colorectal ESD Standardization Implementation Working Group

1. Large sized (>20 mm in diameter) lesions in which en bloc resection using snare EMR is difficult, although it is indicative for endoscopic treatment
   - Lesions showing VI type pit pattern in kudo’s classification
   - Carcinoma with submucosal infiltration
   - Large depressed type lesion
   - Large elevated lesion suspected to be carcinoma
2. Mucosal lesions with fibrosis caused by prolapse due to biopsy or peristalsis of the lesions
3. Sporadic localized tumors in chronic inflammation such as ulcerative colitis
4. Local residual early carcinoma after endoscopic resection

Including granular-type laterally spreading tumors (LST-G), nodular mixed type. EMR, endoscopic mucosal resection.

The primary purpose of ESD is to decrease the risk of local cancer recurrence by performing en bloc R0 resection and to provide a complete pathological specimen. ESD techniques are available using various knives. A standard single channel gastroscope is usually used for ESD. When the lesions are located at the rectum or proximal colon, Q260J endoscope (Olympus Optical) is mostly used. For the lesions located at the distal colon, PCF-Q260II endoscope (Olympus Optical) is used. Injection solutions are glycerol and sodium hyaluronate with small amounts of indigo carmine. Indigo carmine is added to the submucosal injection fluid in order to make a better identifiable blue-colored submucosal layer. It has been recently reported that the use of sodium hyaluronate (Mucolip; Johnson & Johnson, Tokyo, Japan) for submucosal injection provides a longer-lasting submucosal cushion, helping to prevent perforation and make the ESD procedures technically easier and safer. After the submucosal injection, a circumferential incision in the mucosa was made with cutting devices at first. The procedures were primarily performed using a bipolar needle knife (B-knife) (XEMEX Co., Tokyo, Japan) or a monopolar knife (Dual knife, IT knife-2) (Olympus Co., Tokyo, Japan) in our hospital (Fig. 2A, B). The B-Knife were used with the following setting; 50 W, effect 3, Endo-Cut mode, and 30 W, effect 3, Forced coagulation mode with ICC200. The Dual Knife were used with the following setting; 30 W, effect 3, Endo-Cut mode, and 30 W, effect 3, Forced coagulation mode with ICC200. Injection solution was then injected into the submucosal layer to lift the lesion, and the thickened submucosal layer was cut with the same knives. Attachment hood is used in all procedures. A soft transparent hood (JMDN 38819001; Top Corp., Tokyo, Japan) is mounted at the distal end of the gastroscopy in order to optimize the visualization of the operating field in the submucosal space and to create countertraction for exfoliating the submucosal tissue. A small-caliber-tip transparent hood (ST hood; Fujifilm Co., Ltd., Tokyo, Japan) is also useful to lift the incised submucosal tissue and stabilize the submucosal dissection. Conscious sedation by intravenous injection of midazolam (2 mg) was used before the insertion of colonoscope. In addition, 2 mg was given repeatedly, based on the endoscopist’s judgment. In all cases, we used a high-frequency generator unit ICC200 (Erbe Elektromedizim, Tübingen, Germany) and a carbon dioxide (CO2) insufflation system, which is essential for reducing abdominal discomfort.

Clinical outcome of lower GI ESD

We searched PubMed database for publications until July 2012, related to colorectal ESD, using the key words, ESD and colon. The MEDLINE database was also used to search for publications through July 2012 related to ESD, using the above-mentioned keywords. A manual search of the citations of relevant articles was also performed.
Several reports were published from Western countries concerning colorectal ESD, however, compared to Japan it is infrequently performed in Western countries. Uraoka et al reported that there are several differences between practices in Japan and Western countries. Uraoka et al reported that there are several differences between practices in Japan and infrequently performed in Western countries. Uraoka et al reported that there are several differences between practices in Japan and infrequently performed in Western countries.

**Lower GI ESD in Western countries**

Several reports were published from Western countries concerning colorectal ESD, however, compared to Japan it is infrequently performed in Western countries. Uraoka et al reported that there are several differences between practices in Japan and Western countries. At first, according to the measurement of colonic length of Asian and Caucasian patients, the colonic length of Caucasian patients was significantly longer. In the clinical setting, short-type (1.3 m) colonoscopes are regularly used in Japan, whereas in most Western countries, long (1.7 m) colonoscopes are used. Therefore, a more difficult colonic anatomy and the frequent need for longer colonoscopes would support the possibility that colonoscopy and related therapeutic procedures are more complex in Western patients. Second, Western endoscopists prefer to use propofol for sedation during colonoscopy. If the position of the patient is not going to be changed during colonoscopy, then stronger sedation can be used. However, taking advantage of gravitation during colonoscopy is useful, as the submucosal dissection plane can be observed more clearly in certain patient positions, in which the partially dissected lesion is pulled down by its own weight. Patient rotation can be used by Japanese endoscopists during colorectal ESD, because they do not apply deep sedation to their patients. One of the main limitations to the implementation of ESD in Western countries is that, compared to Japan, there are very few institutions with enough expertise in colorectal ESD to become training centers. However, in Japan, a significant number of endoscopists have experience, at a minimum, in more than 50 colorectal ESD cases. Furthermore, development of various devices, specialized in each part of the digestive tract, was regarded as the major factor why the ESD procedure is widely practiced in Japan. Performing ESD in a clinical setting with appropriate professional guidance and supervision also is an important consideration in terms of the learning curve, at least in the early phases of actual clinical experience.

In the future, establishment of a training system for colorectal ESD, based on clinical outcomes and the learning curves for trainees, is necessary to standardize training and achieve wider acceptance of the technique.

**References**


