

EDITORIAL

Endoscopic submucosal dissection for gastrointestinal neoplasms

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Abstract

Endoscopic submucosal dissection (ESD) is an advanced technique of therapeutic endoscopy for superficial gastrointestinal neoplasms. Three steps characterize it: injecting fluid into the submucosa to elevate the lesion, cutting the surrounding mucosa of the lesion, and dissecting the submucosa beneath the lesion. The ESD technique has rapidly permeated in Japan for treatment of early gastric cancer, due to its excellent results of en-bloc resection compared to endoscopic mucosal resection (EMR). Although there is still room for improvement to lessen its technical difficulty, ESD has recently been applied to esophageal and colorectal neoplasms. Favorable short-term results have been reported, but the application of ESD should be well considered by three aspects: (1) the possibility of nodal metastases of the lesion, (2) technical difficulty such as location, ulceration and operator's skill, and (3) organ characteristics.

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INTRODUCTION

Application of endoscopic resection (ER) to gastrointestinal (GI) neoplasms is limited to lesions with no risk of nodal metastasis. Either polypectomy or endoscopic mucosal resection (EMR) is beneficial for patients because of its low level of invasiveness. However, to ensure the curative potential of these treatment modalities, accurate histopathologic assessment of the resected specimens is essential because the depth of invasion and lymphovascular infiltration of the tumor is associated with considerable risk for lymph node metastasis. For accurate assessment of the appropriateness of the therapy, en bloc resection is more desirable than piecemeal resection. For a reliable en bloc resection of GI neoplasms, a new method of ER called endoscopic submucosal dissection (ESD) has been developed. In this article, an outline of the current status of ESD will be discussed.

DEVELOPMENT OF ESD

The ESD technique has developed from one of the EMR techniques, namely endoscopic resection after local injection of a solution of hypertonic saline-epinephrine (ERHSE)^[1]. Initially, the ESD technique was called by various names such as cutting EMR, exfoliating EMR, EMR with circumferential incision *etc.* However, a new name was proposed to this technique in 2003, as a treatment positioned between EMR and laparoscopic surgery, since this technique is innovative and enables complete resection of neoplasms that were impossible to resect en bloc by EMR.

At present, numerous electro-surgical knives such as insulation-tipped diathermic knife (IT-knife)^[2-6], needle knife^[7], hook knife^[8], flex knife^[9-11], triangle-tipped knife^[12], flush knife^[13], mucosectomy^[14], splash needle^[15] and a special device called a small-caliber tip transparent (ST) hood^[7] are available for this technique. One or two of these electro-surgical knives are used in combination with a high frequency electro-surgical current (HFEC) generator with an automatically controlled system (Endocut mode, Erbotom ICC200, ICC350, VIO300D, ERBE, Tubingen, Germany) (PSD-60, Olympus, Tokyo, Japan). New types of endoscopes are available for ESD, such as an endoscope with a water jet system (EG-2931, Pentax, Tokyo, Japan, GIF-Q260J, Olympus, Tokyo, Japan), an endoscope with a multi-bending system (M-scope: XGIF-Q240M, R-scope: XGIF-2TQ240R, Olympus, Tokyo, Japan) to facilitate the ESD procedure^[16-19]. As another approach to successful

ESD, investigations of submucosal injection solutions have been actively done. It was reported that a hyaluronic acid solution makes a better long-lasting submucosal cushion without tissue damage than other available solutions^[7,20-23]. As a further improvement of hyaluronic acid solution, usefulness of a mixture of high-molecular-weight hyaluronic acid, glycerin, and sugar has also been reported^[24,25].

ESD is characterized by three steps: injecting fluid into the submucosa to elevate the lesion from the muscle layer, circumferential cutting of the surrounding mucosa of the lesion, and subsequent dissection of the connective tissue of the submucosa beneath the lesion. Major advantages of this technique in comparison with polypectomy or EMR are as follows. The resected size and shape can be controlled, en bloc resection is possible even in a large neoplasm, and neoplasms with submucosal fibrosis are also resectable. So this technique can be applied to the resection of complex neoplasms such as large neoplasms, ulcerative non-lifting neoplasms, and recurrent neoplasms. The disadvantages of this technique are the requirement of two or more assistants, it is time-consuming, there is a higher risk of bleeding and perforation than EMR. In Japan, ESD is now gaining acceptance as the standard endoscopic resection technique for stomach neoplasms in an early stage, especially for large or ulcerative neoplasms. Recently, the ESD technique is applied to esophageal or colorectal neoplasms in some institutions, although it is still controversial considering the technical difficulty, associated risks, and favorable outcomes by EMR.

INDICATION FOR ENDOSCOPIC RESECTION

Gastric cancer

Early gastric cancer (EGC) is defined to a mucosal or submucosal invasive cancer (T1 cancer) irrespective of the presence of lymph node metastasis. Lesions indicated for ER should be EGC with no risk of nodal metastasis and that can be resected in a single fragment. Using a large database of more than 5000 EGC patients who underwent gastrectomy with D2 lymph node dissection, a criteria of node negative cancer has been defined^[26]. At present, lesions with preoperative endoscopic diagnosis of differentiated type intramucosal cancer without ulcer findings, differentiated type intramucosal cancer no larger than 3 cm in diameter with ulcer findings, differentiated type minute invasive submucosal (less than 500 micrometers below muscularis mucosa) cancer no larger than 3 cm in diameter are considered as expanding indication for ER^[27]. Undifferentiated type cancer lesions, and preoperative diagnosis of ulcerative findings is difficult, so that ER for these lesions should be carefully considered.

Esophageal cancer

Early esophageal cancer (EEC) involving the epithelium (m1: carcinoma in situ) or the lamina propria (m2) are candidates for ER because no lymph node metastasis have been reported in cancers limited to these two layers^[28]. For EEC invading the muscularis mucosa (m3), the lymph

node metastasis rate is reported as 9%, and for cancer with minute submucosal invasion (< 200 micrometers below the muscularis mucosa; sm1) the rate is 19%^[29]. The lymph node metastasis rate of m3 or sm1 cancer without lymphovascular infiltration of the tumor is reported as 4.7%^[29]. Therefore, for patients unwilling for esophagectomy or patients with comorbid diseases not suited for surgery, ER may be a relative indication for m3 or sm1 cancer. Also, for lesions spreading more than three-quarter of circumference of the esophagus are considered as relative indication for ER because post-operative stricture occurs in a high rate.

Colorectal cancer

Early colorectal cancer (ECC) limited to the mucosa or with slight submucosal invasion (< 1000 micrometers below the muscularis mucosa; sm1) are candidates for ER^[30]. However, even for lesions that meet the criteria above, laparoscopic or open surgery may be selected in some institutions considering the location and size of the lesion. In institutions actively performing ESD for colorectal lesions, depressed lesions and laterally spreading tumors of non-granular type (LST-NG) are considered as good candidates for ESD because these lesions have a high possibility of submucosal invasion which may be difficult to diagnose preoperatively, and a thorough histopathological assessment of the resected specimen is essential.

Preoperative evaluation for candidates of ER

Endoscopy with chromoendoscopy is essential to define the lesion. To evaluate the depth of the lesion, size, redness, presence or absence of ulceration, superficial structure of the lesion, and deformity of the wall of the organ in compliance with air-flow rate are carefully observed by endoscopy and chromoendoscopy. Magnification endoscopy with narrow band imaging technique (NBI) has been reported as a promising new modality to evaluate the depth of EEC. Magnification endoscopy with NBI is also useful to distinguish the border of EGC in case of lack of utility of chromoendoscopy with indigocarmine. Magnification endoscopy with crystal violet staining or NBI is useful in estimating the depth of colorectal lesions. Endoscopic ultrasonography is often performed to evaluate the depth of invasion, and computed tomography may be performed to detect lymph node metastasis if any, if the diagnosis of node negative cancer is difficult to judge even with multiple diagnostic modalities.

Pathological evaluation of the removed specimen

Whether a lesion may be included into the criteria of node-negative neoplasms is considered before treatment. However, at present, it is impossible to make a definite diagnosis of a neoplasm regarding depth, histological type and lymphatic vessel invasion before treatment. It is often experienced that although a biopsy specimen shows adenoma/dysplasia of a lesion, a diagnosis of cancer is made after total resection of the lesion. Therefore, a precise pathological evaluation of the resected specimen is essential, and an en bloc resection of the lesion is desirable in this respect.

After removal, the specimen should be oriented immediately before it is immersed in formalin. Orientation of the specimen is accomplished by fixing the periphery with thin needles on a plate of rubber or wood. The submucosal side of the specimen is faced to the plate. After fixation, the specimen is sectioned serially at 2 mm intervals parallel to a line that includes the closest part between the margin of the specimen and of the neoplasm, so that both lateral and vertical margins are assessed. The depth of invasion is then evaluated microscopically along with the degree of differentiation and lymphovascular infiltration, if any.

In result of thorough pathological assessment, if the lesion is resected en bloc with negative margins of neoplasm and fulfills the criteria of node-negative neoplasms with no lymphovascular infiltration, the treatment is judged as curative resection. For lesions with piecemeal resection but being judged as node-negative neoplasms, or lesions with histologically non-evaluable areas due to artifact or tissue burning, a periodical endoscopic follow-up should be performed to detect residual neoplasm or local recurrence. On the other hand, for lesions that do not fulfill the criteria of node-negative neoplasms, additional surgery with nodal dissection should be strongly recommended.

OUTCOMES OF ESD

En bloc resection rate

Recent results of en bloc resection rate and local recurrence of ESD for neoplasms in the stomach, esophagus and colorectum are described in Table 1. For gastric neoplasms larger than 20 mm, en bloc resection rate is extremely low among conventional EMR methods, and local recurrence rates are around 10%^[44]. Although ESD was considered as a difficult and complicated technique when it was first described in the stomach, after maturity of the techniques of ESD, en bloc resection rates became greater than 90%, regardless of size, and local recurrence rates became almost zero. Technical feasibility and favorable results of ESD have also been reported in recurrent neoplasms^[45-47], neoplasms of the esophago-gastric junction^[48], and duodenal neoplasms although the number of cases is small. Few reports of ESD for resection of subepithelial tumors have also been published^[49].

Complication

Complications of ESD include pain, bleeding, perforation, and stricture. Pain after ESD is often mild and lasts one or two days after the procedure although the frequency is low. Patients of esophageal ESD are more likely to develop pain than gastric or colorectal ESD.

Complications of post-operative bleeding and perforation among various ESD methods in the stomach, esophagus and colorectum are described in Table 2. Bleeding is more frequent in the stomach cases, whereas perforation is more frequent in the colorectal cases. To prevent post-procedural bleeding, hemostasis of appearing vessels on the artificial ulcer after removing the specimen is essential. Hemostasis is performed by hemostatic forceps (HDB2422/HDB2418, Pentax), coagrasper (FD-410LR,

Table 1 Recent outcomes of various endoscopic submucosal dissection methods for stomach, esophagus and colorectum

Site	Author	Yr	Method	En bloc resection rate (%)	Local recurrence rate (%)
Stomach	Yamamoto ^[33]	2002	EMRSH	76 (53/70)	3 (2/67)
	Ishigooka ^[34]	2004	s-ERHSE	79 (27/34)	0 (0/34)
	Oda ^[35]	2005	ESD-IT knife	93 ¹ (957/1033)	-
	Kakushima ^[32]	2006	ESD-Flex knife	91 ¹ (347/383)	-
	Imagawa ^[36]	2006	ESD-Flex knife	84 ¹ (181/195)	0 (0/164)
	Oyama ^[37]	2006	ESD-Hook knife	94 (104/111)	0 (0/111)
	Onozato ^[38]	2006	ESD-Flex knife	94 ¹ (161/171)	0 (0/99)
Esophagus	Hirasaki ^[39]	2007	ESD-IT knife	96	-
	Oyama ^[8]	2005	ESD-Hook knife	95 (95/102)	0 (0/102)
	Fujishiro ^[11]	2006	ESD-Flex knife	100 (58/58)	2.5 (1/40)
Colorectum	Fujishiro ^[31]	2007	ESD-Flex knife	91.5 (183/200)	1.8 (2/111)
	Saito ^[40]	2007	ESD several knives	84 (168/200)	0.5 (1/180)
	Tanaka ^[41]	2007	ESD several knives	80 (56/70)	0 (0/62)
	Tamegai ^[42]	2007	ESD-Hook knife	98.6 (33/42)	11 (4/36)
	Onozato ^[43]	2007	ESD-Flex knife	77 (27/35)	0 (0/23)

¹En bloc resection + R0 resection rate.

Olympus), hot biopsy forceps, argon plasma coagulation or endoclips. According to perforation, recent case series suggest that small perforation immediately recognized can be successfully sealed with endoclips and treated conservatively by nasogastric suction, fasting and antibiotics without emergency laparotomy^[51,52]. However, there are rare cases of delayed perforation, which requires surgical rescue. Delayed perforation may occur in the esophagus, stomach, duodenum and colorectum^[31,53-56], mostly at two or more days after a successful ESD. The reason for delayed perforation is unknown, however patients with uncontrolled diabetes mellitus, patients on permanent hemodialysis, lesions located on surgical anastomosis, and too much coagulation are considered as possible risk factors.

Stricture after ESD may occur in esophageal ESD when the ESD ulcer is larger than two-third of circumference of the esophageal lumen, or in gastric ESD when the ESD ulcer involves more than three quarter of the pylorus or pre-pylorus area. In these cases, early intervention to avoid passage obstruction is required. Dilation using bougie or balloon are often applied one week after ESD and repeated several times until healing of the ESD ulcer^[8,11,57].

MANAGEMENTS AFTER ESD

In Japan, ESD is performed on hospitalized patients. After ESD, eating is usually started on the next or 2 d after ESD if there is no complication, and the patient

Table 2 Bleeding and perforation rate of various endoscopic submucosal dissection methods for stomach, esophagus and colorectum

Site	Author	Year	Method	Total cases	Bleeding (%)	Perforation (%)
Stomach	Yamamoto ^[33]	2002	EMRSH	70	4	0
	Ishigooka ^[34]	2004	s-ERHSE	34	0	12
	Oda ^[35]	2005	ESD-IT knife	1033	6	4
	Kakushima ^[32]	2006	ESD-Flex knife	383	3.4	3.9
	Imagawa ^[36]	2006	ESD-Flex knife	159	0	6.1
	Oyama ^[37]	2006	ESD-Hook knife	111	-	1
	Onozato ^[38]	2006	ESD-Flex knife	171	7.6	3.5
	Hirasaki ^[39]	2007	ESD-IT knife	112	4	1
	Esophagus	Oyama ^[8]	2005	ESD-Hook knife	102	-
Fujishiro ^[11]		2006	ESD-Flex knife	58	0	6.9
Colorectum	Fujishiro ^[31]	2007	ESD-Flex knife	200	1	6
	Saito ^[40]	2007	ESD-several knives	200	2	5
	Tanaka ^[41]	2007	ESD-several knives	70	1.4	10
	Tamegai ^[42]	2007	ESD-Hook knife	74	-	1.4
	Hurlstone ^[50]	2007	ESD-Flex knife	42	12	2.4
	Onozato ^[43]	2007	ESD-Flex knife	35	0	2.9

may be discharged within a few days. Antacids are usually administered to gastric and esophageal ESD patients to relieve pain, prevent postoperative bleeding and promote ulcer healing. A recent study showed that proton pump inhibitors more effectively prevented bleeding from the gastric ulcer created after ESD than did H₂-receptor antagonists^[58]. Ulcers after ESD are reported to heal within 6 to 8 wk in the esophagus, stomach and colorectum^[59-63].

Endoscopic surveillance should be carried out in patients after ESD not only to detect local recurrence but also metachronous cancer especially in the esophagus and stomach. A recent study showed that the average time to detect a first metachronous gastric cancer (MGC) was 3.1 ± 1.7 years after EMR/ESD, and the cumulative 3-year incidence was 5.9%^[64]. In order to detect MGC at an early stage to perform a successful ER, annual endoscopic surveillance program may be practical for post-ER patients.

LONG-TERM OUTCOMES AFTER ESD

Long-term outcomes after ESD for gastric cancers within the expanded indication are currently under investigation. Survival data is still lacking in the literature, however in the 2007 annual meeting of Japanese gastroenterological endoscopy society (JGES), a symposium was held upon long-term outcomes after gastric and esophageal ESD. For gastric ESD, 3-year disease free survival rate was reported as 90%-92%, local recurrence rate was reported as 0.8%-12%. For lesions within the criteria of node negative cancers, there were no reports of distant metastasis. Metachronous gastric cancer detection rate during follow-up was reported as 3.4%-10.2%. In comparison, long-term outcomes after EMR for small differentiated mucosal EGC less than 20 mm in diameter have been reported as comparable to those after gastrectomy. The disease-specific 5- and 10-year survival rates were 99% and 99%^[65]. For esophageal ESD, in the 2007 JGES meeting, 3-year survival rate for m1-2 cancer and m3-sm1 cancer were 95.1% and 86.7%, respectively. According to colorectal ESD, there is still no long-term data at present.

FUTURE PERSPECTIVES

With the development of ESD, more than half of GI cancers in the early stage are removed by ER in advanced institutions in Japan. En bloc retrieval of lesions is essential for detailed histopathologic studies, which form the basis for stratification of treatment outcomes and patient's prognosis. ESD theoretically offers greater histopathological accuracy than conventional EMR methods or piecemeal resection. However, ESD requires highly skilled endoscopists, and a suitable training program is demanded for permeation of this technique. For trainees starting ESD, skills of routine endoscopy and colonoscopy, target biopsy, endoscopic hemostasis techniques and simple EMR techniques should be required. A trainee would gain early proficiency of ESD after 30 cases under supervision of a mentor^[32,66]. On the other hand, serious complications such as delayed perforation have been reported, and a thorough patient care before and after ESD is essential. At present, selection of a lesion within the criteria for ER, selection of the patient with adequate general function should be well considered. It is important to share the information and experience among endoscopists to skill up and avoid serious complications. The ESD technique is still not a treatment at ease, and further refinements of the technique is required to popularize ESD as a safe and reliable, less invasive treatment for patients with GI neoplasms.

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