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TOPIC HIGHLIGHT

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Endoscopic submucosal dissection for superficial esophageal neoplasms

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Abstract

Endoscopic submucosal dissection (ESD) is currently accepted as the major treatment modality for superficial neoplasms in the gastrointestinal tract including the esophagus. An important advantage of ESD is its effectiveness in resecting lesions regardless of their size and severity of fibrosis. Based on excellent outcomes for esophageal neoplasms with a small likelihood of lymph node metastasis, the number of ESD candidates has increased. On the other hand, ESD still requires highly skilled endoscopists due to technical difficulties. To avoid unnecessary complications including perforation and postoperative stricture, the indications for ESD require careful consideration and a full understanding of this modality. This article, in the highlight topic series, provides detailed information on the indication, procedure, outcome, complications and their prevention in ESD of superficial esophageal neoplasms.

Key words: Complications; Endoscopic submucosal dissection; Esophageal neoplasm; Indication; Outcome; Squamous cell carcinoma

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INTRODUCTION

Endoscopic submucosal dissection (ESD), which was developed for stomach neoplasms[1-3], has also been accepted as an established procedure for superficial neoplasms of the esophagus. The most important advantage of ESD is its effectiveness in resecting large-sized lesions in an *en bloc* fashion, as conventional endoscopic mucosal resection (EMR) sometimes results in piece-meal resection followed by a high rate of local recurrence[4]. ESD theoretically enables the resection of lesions regardless of their size and severity of fibrosis. Based on previously reported excellent outcomes, the number of ESD candidates with esophageal neoplasms have increased similar to those with stomach neoplasms undergoing ESD[5,6]. In this review, an outline of the current status of ESD for esophageal neoplasms is described.

INDICATIONS

As with candidates suffering from other gastrointestinal

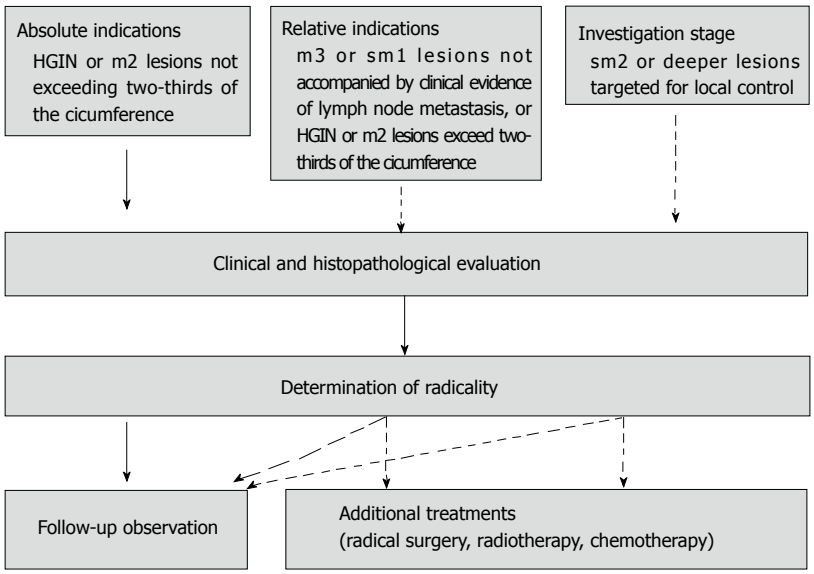

Figure 1 Indication for endoscopic resection in the Japan Esophageal Society guideline.

tract diseases, patients scheduled for esophageal ESD are determined by two factors: a small likelihood of lymph node metastasis and technical resectability.

The former was determined by a large number of surgical resection cases with extensive histological investigations[7,8]. These studies showed that high-grade intraepithelial neoplasms (HGINs), including noninvasive squamous cell carcinomas (SCCs) (carcinoma *in situ*, m1) and intramucosal invasive SCCs limited to the lamina propria mucosae (m2) without vessel infiltration have no lymph node or distant metastases. Accordingly, in the national guideline of the Japan Esophageal Society (JES), these are allocated to absolute indication of endoscopic local resection including ESD[9]. Deeper lesions of 200 μm in the submucosa (m3 and sm1) are allocated to relative indication because they have a probability of lymph node metastasis of 10%-15% (Figure 1).

The latter depends principally on circumferential extension. In the JES guideline, absolute indication is limited to lesions of less than two-thirds of the circumferential extension. Lesions of more than two-thirds of the circumferential extension are allocated to relative indication. Circumferential extension not only affects technical resectability but also the risk of postoperative stricture after ESD, as mentioned below[10,11]. In this regard, ESD can minimize the risk of unnecessary postoperative stricture by precisely controlling the resected area. This is another advantage of ESD in avoiding excessive resection compared with conventional EMR.

Therefore, considering the above factors, we decided that in patients with lesions allocated to relative indication general status and comorbidities should be considered.

On the other hand, the indication for ESD of esophageal adenocarcinoma is still controversial because the incidence of esophageal adenocarcinoma is extremely low in Japan where ESD is widely performed. However, Hirasawa *et al*[12] reported a promising long-term outcome after ESD for differentiated adenocarcinoma of the esophagogastric junction limited to a depth of invasion of 500 μm in the submucosa. In this regard, ESD for esophageal adenocarcinoma might also be acceptable although further research data is mandatory especially in Western countries.

PROCEDURES

ESD requires special electrosurgical knives, such as the insulated-tipped (IT) knife, the flex knife, the hook knife, the triangle-tip (TT) knife, and the dual knife[2,13,14]. The results obtained using each of these electrosurgical knives are similar to those in patients with stomach neoplasms. Therefore, selection of these knives depends mainly on operator preference and expertise. Of these knives, we mostly use the dual knife (KD-650L, Olympus) for ESD of the esophagus. The knife is fixed at a length of 2 mm during procedures.

We mainly use a slim, single-channel, high-definition endoscope with a water-jet system (GIF-Q260J; Olympus, Tokyo, Japan) and a high frequency generator (VIO300; ERBE Elektromedizin, Tübingen, Germany) with a special cutting mode and coagulation current, as mentioned below. The transparent attachment is fitted to the top of the endoscope to maintain a constant endoscopic view and to create counter-traction on connective tissue during dissection.

In our recent ESD procedures, patients underwent ESD under conscious sedation using periodic intravenous administration of diazepam (in total, 0.1-0.5 mg/kg body weight) and pentazocine (in total, 0.3-0.7 mg/kg body weight) or under general anesthesia with careful consideration of the estimated operation time, location of the lesion, and general status of the patient. Prophylactic antibiotics are not administered routinely as there is no evidence for their use during the periendoscopic

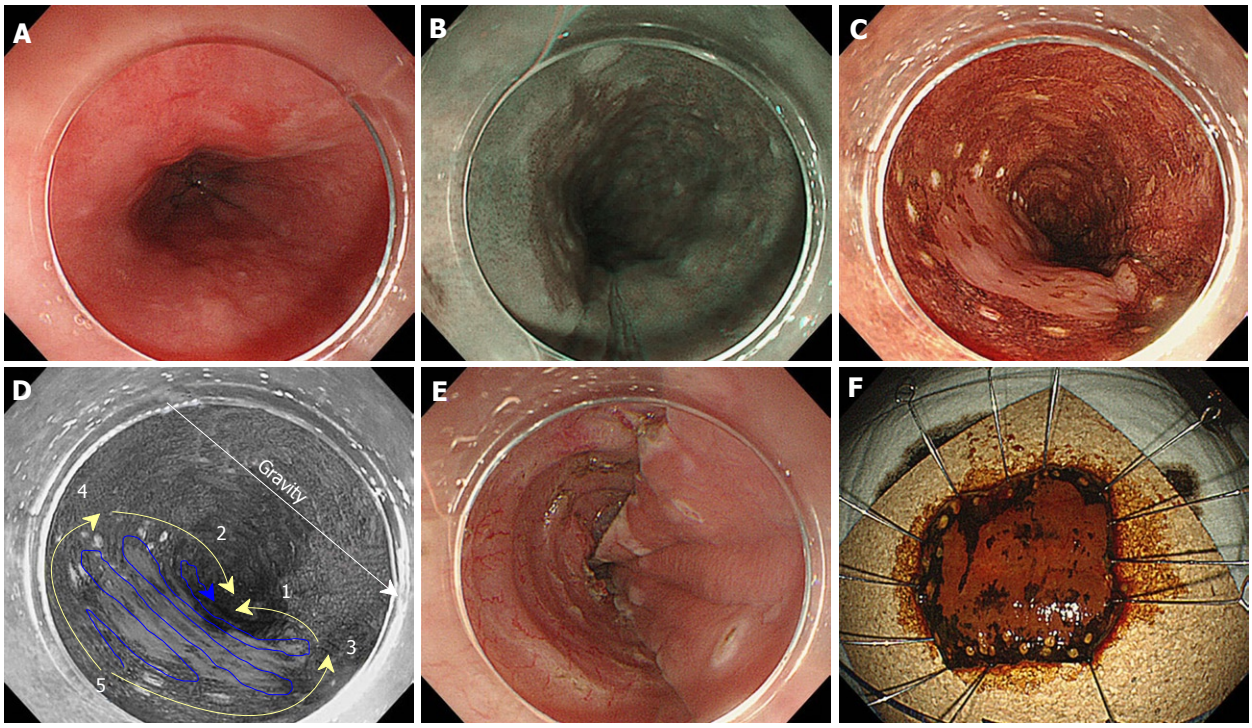

Figure 2 Endoscopic submucosal dissection of an esophageal neoplasm. A: The reddish mucosa in the anterior wall of the middle thoracic esophagus shown by conventional endoscopy with white light; B: The brownish mucosa in one-third of the circumferential extension shown by endoscopy with narrow band imaging; C: Marking around the lesion under chromoendoscopy with iodine staining to demarcate the lesion; D: Mucosal incision at the anal side (yellow line 1-2), followed by incision at the oral side (yellow line 3-4). Incision is made from the lower side to lift it up from the collection of fluid taking gravity into consideration. After circumferential incision, dissection of the submucosa is begun from the oral end to the anal end (blue line 5); E: Artificial ulcer after removal of the lesion; F: Resected specimen in an *en bloc* fashion.

period. Second-generation cephalosporins are only administered during a few days of fasting in cases with perforation.

ESD procedures in the esophagus are principally the same as those in other areas of the gastrointestinal tract. They consist of four steps; marking, lifting, incision and dissection (Figure 2). For marking around the lesion, dots are placed about 5 mm outside the lesion using soft coagulation mode (effect 5, output 50 W). To demarcate the lesion margin, narrow band imaging with magnifying endoscopy and Lugol staining are very useful. In lifting, we mainly use 0.4% hyaluronic acid preparation (MucoUp; Johnson and Johnson KK, Tokyo, Japan) double diluted with normal saline for submucosal injection to lift the lesion up from the muscular layer. Approximately 2 mL solution is injected into the submucosa, and the injection is repeated several times until the mucosa is lifted to an acceptable level. An incision in the mucosa around the lesion is made using cutting mode (Endocut I, effect 3, duration 3, interval 3). The anal half of the incision which is horseshoe-shaped is completed first, followed by the oral half. Incision from the left-wall side is preferable with consideration of gravity as submerging the lesion in the collection of fluid can disturb the endoscopic view. Dissection of the submucosa is begun from the oral end to the anal end using swift coagulation mode (effect 4, output 40 W). It is also mandatory to control minor bleeding because this can also disturb the endoscopic view. To control bleeding, hemostatic forceps are used in soft coagulation mode (effect 5, 50 W). The water-jet system is also useful to maintain a clear view and to treat visible bleeding vessels.

OUTCOMES AND COMPLICATIONS

Outstanding *en bloc* resection rates (90%-100%), curative resection rates (88%-97%), and low rates of major complications (perforation, 0-6%; bleeding, 0%) have been reported as shown in Table 1[14-18]. In a previous comparative study of conventional EMR and ESD, ESD was reported to be more reliable in achieving curative resection due to the higher local recurrence rate after conventional EMR[4]. Although perforation can be a substantial risk, our experience has shown that cases of minor perforation can recover well following conservative treatment if noticed as soon as it occurs. With regard to long-term outcomes, the cause-specific survival rates at 5 years for patients with HGINs/m2 SCCs and m3/sm SCCs are reported to be 100% and 85%, respectively[18]. These survival rates are consistent with the findings of a comparative study of conventional EMR and surgical resection[19]. Considering the higher comorbidities of esophagoectomy and the higher incidence of incomplete resection by conventional EMR[4,20], ESD is accepted as a superior treatment option for esophageal squamous cell neoplasms.

Table 1 Recent outcomes for endoscopic submucosal dissection of esophageal neoplasms

Author	Yr	Electrosurgical knife	*En bloc* resection rate	Local recurrence rate	Perforation
Oyama[14]	2005	Hook knife	95% (95/102)	0% (0/102)	6% (6/102)
Ishihara[17]	2008	Hook knife	100% (31/31)	0% (31/31)	3% (1/31)
Ono[18]	2009	Flex knife or Splash needle	100% (107/107)	1% (1/87)	4% (4/107)
Repici[16]	2010	Hook knife	90% (18/20)	0% (0/20)	10% (2/20)
Ishii[15]	2010	Flex knife or Hook knife	100% (37/37)	0% (0/37)	0% (0/37)

On the other hand, postoperative stricture has arisen as a major concern during long-term follow-up because postoperative stricture can compromise patient quality of life. Almost all semicircular resections can cause postoperative stricture shortly after ESD[10,18]. Although various effective preventive treatments have been reported including balloon dilatation, and local injection or systemic administration of steroids[21-24], there is still no solid protocol for preventive treatment. In addition, perforation during dilatation for esophageal stricture is reported to be another risk[25].

FUTURE PERSPECTIVES

ESD has been proved to be a promising technique for esophageal neoplasms. Although there is a substantial risk of perforation and postoperative stricture, these are preventable complications. However, ESD techniques still require highly skilled endoscopists. To prevent severe complications and to popularize ESD as a safe and easy treatment, further advances in the technique and protocol during the periendoscopic period is mandatory.

In terms of the prevention of perforation, effective use of ESD and conventional EMR is important to minimize unnecessary perforation. Ishihara *et al*[17] reported that no significant differences were found between *en bloc* and curative resection rates in EMR using a transparent cap (EMR-C) and ESD in lesions less than 15 mm. They also proposed that ESD may be the best method for lesions more than 20 mm. In other words, EMR-C might be an effective substitute for treating lesions less than 15 mm, depending on the general status of the patient and skill-level of the endoscopist.

In terms of the prevention of postoperative stricture, more evidence is needed to identify high-risk patients and to treat them appropriately. In this regard, a predictive flowchart which we previously proposed might be an option in coping with this problem[11]. In addition, new technologies, such as a biodegradable stent or an autologous mucosal epithelial sheet, may be a breakthrough in overcoming postoperative stricture[26,27].

Undoubtedly, the final goal of ESD for esophageal neoplasms is not to resect the lesions in an *en bloc* fashion, but to prevent the patient dying of esophageal cancer without unnecessary risks. To achieve this goal, standardization of ESD procedures including preventive protocols for complications during the periendoscopic period should be established as soon as possible.

REFERENCES

1 **Yamamoto H**, Kawata H, Sunada K, Satoh K, Kaneko Y, Ido K, Sugano K. Success rate of curative endoscopic mucosal resection with circumferential mucosal incision assisted by submucosal injection of sodium hyaluronate. *Gastrointest Endosc* 2002; **56**: 507-512

2 **Yahagi N**, Fujishiro M, Kakushima N, Kobayashi K, Hashimoto T, Oka M, Iguchi M, Enomoto S, Ichinose M, Niwa H and Omata M. Endoscopic submucosal dissection for early gastric cancer using the tip of an electrosurgical snare (thin type). *Dig Endosc* 2004; **16**: 34-38

3 **Oda I**, Gotoda T, Hamanaka H, Eguchi T, Saito Y, Matsuda T, Bhandari P, Emura F, Saito D and Ono H. Endoscopic submucosal dissection for early gastric cancer: technical feasibility, operation time and complications from a large consecutive series. *Dig Endosc* 2005; **17**: 54-58

4 **Katada C**, Muto M, Manabe T, Ohtsu A, Yoshida S. Local recurrence of squamous-cell carcinoma of the esophagus after EMR. *Gastrointest Endosc* 2005; **61**: 219-225

5 **Gotoda T**. Endoscopic resection of early gastric cancer. *Gastric Cancer* 2007; **10**: 1-11

6 **Goto O**, Fujishiro M, Kodashima S, Ono S, Omata M. Outcomes of endoscopic submucosal dissection for early gastric cancer with special reference to validation for curability criteria. *Endoscopy* 2009; **41**: 118-122

7 **Natsugoe S**, Baba M, Yoshinaka H, Kijima F, Shimada M, Shirao K, Kusano C, Fukumoto T, Mueller J, Aikou T. Mucosal squamous cell carcinoma of the esophagus: a clinicopathologic study of 30 cases. *Oncology* 1998; **55**: 235-241

8 **Tajima Y**, Nakanishi Y, Ochiai A, Tachimori Y, Kato H, Watanabe H, Yamaguchi H, Yoshimura K, Kusano M, Shimoda T. Histopathologic findings predicting lymph node metastasis and prognosis of patients with superficial esophageal carcinoma: analysis of 240 surgically resected tumors. *Cancer* 2000; **88**: 1285-1293

9 **Kuwano H**, Nishinuma Y, Ohtsu A, Kato H, Kitagawa Y, Tamai S, Toh Y and Matsubara H. Guidelines for diagnosis and treatment of carcinoma of the esophagus. April 2007 edition: part I. Edited by the Japan Esophageal Society. *Esophagus* 2008; **5**: 61-73

10 **Mizuta H**, Nishimori I, Kuratani Y, Higashidani Y, Kohsaki T, Onishi S. Predictive factors for esophageal stenosis after endoscopic submucosal dissection for superficial esophageal cancer. *Dis Esophagus* 2009; **22**: 626-631

11 **Ono S**, Fujishiro M, Niimi K, Goto O, Kodashima S, Yamamichi N, Omata M. Predictors of postoperative stricture after esophageal endoscopic submucosal dissection for superficial squamous cell neoplasms. *Endoscopy* 2009; **41**: 661-665

12 **Hirasawa K**, Kokawa A, Oka H, Yahara S, Sasaki T, Nozawa A, Tanaka K. Superficial adenocarcinoma of the esophagogastric junction: long-term results of endoscopic submucosal dissection. *Gastrointest Endosc* 2010; **72**: 960-966

13 **Ohkuwa M**, Hosokawa K, Boku N, Ohtu A, Tajiri H, Yoshida S. New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. *Endoscopy* 2001; **33**: 221-226

14 **Oyama T**, Tomori A, Hotta K, Morita S, Kominato K, Tanaka M, Miyata Y. Endoscopic submucosal dissection of early esophageal cancer. *Clin Gastroenterol Hepatol* 2005; **3**: S67-S70

15 **Ishii N**, Horiki N, Itoh T, Uemura M, Maruyama M, Suzuki S, Uchida S, Izuka Y, Fukuda K, Fujita Y. Endoscopic submucosal dissection with a combination of small-caliber-tip transparent hood and flex knife is a safe and effective treatment for superficial esophageal neoplasias. *Surg Endosc*

2010; **24**: 335-342
16 **Repici A**, Hassan C, Carlino A, Pagano N, Zullo A, Rando G, Strangio G, Romeo F, Nicita R, Rosati R, Malesci A. Endoscopic submucosal dissection in patients with early esophageal squamous cell carcinoma: results from a prospective Western series. *Gastrointest Endosc* 2010; **71**: 715-721
17 **Ishihara R**, Iishi H, Uedo N, Takeuchi Y, Yamamoto S, Yamada T, Masuda E, Higashino K, Kato M, Narahara H, Tatsuta M. Comparison of EMR and endoscopic submucosal dissection for en bloc resection of early esophageal cancers in Japan. *Gastrointest Endosc* 2008; **68**: 1066-1072
18 **Ono S**, Fujishiro M, Niimi K, Goto O, Kodashima S, Yamamichi N, Omata M. Long-term outcomes of endoscopic submucosal dissection for superficial esophageal squamous cell neoplasms. *Gastrointest Endosc* 2009; **70**: 860-866
19 **Shimizu Y**, Tsukagoshi H, Fujita M, Hosokawa M, Kato M, Asaka M. Long-term outcome after endoscopic mucosal resection in patients with esophageal squamous cell carcinoma invading the muscularis mucosae or deeper. *Gastrointest Endosc* 2002; **56**: 387-390
20 **Shimura T**, Sasaki M, Kataoka H, Tanida S, Oshima T, Ogasawara N, Wada T, Kubota E, Yamada T, Mori Y, Fujita F, Nakao H, Ohara H, Inukai M, Kasugai K, Joh T. Advantages of endoscopic submucosal dissection over conventional endoscopic mucosal resection. *J Gastroenterol Hepatol* 2007; **22**: 821-826
21 **Ezoe Y**, Muto M, Horimatsu T, Morita S, Miyamoto S, Mochizuki S, Minashi K, Yano T, Ohtsu A, Chiba T. Efficacy of preventive endoscopic balloon dilation for esophageal stricture after endoscopic resection. *J Clin Gastroenterol* 2011; **45**: 222-227
22 **Yamaguchi N**, Isomoto H, Nakayama T, Hayashi T, Nishiyama H, Ohnita K, Takeshima F, Shikuwa S, Kohno S, Nakao K. Usefulness of oral prednisolone in the treatment of esophageal stricture after endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. *Gastrointest Endosc* 2011; **73**: 1115-1121
23 **Kochhar R**, Makharia GK. Usefulness of intralesional triamcinolone in treatment of benign esophageal strictures. *Gastrointest Endosc* 2002; **56**: 829-834
24 **Altintas E**, Kacar S, Tunc B, Sezgin O, Parlak E, Altiparmak E, Saritas U, Sahin B. Intralesional steroid injection in benign esophageal strictures resistant to bougie dilation. *J Gastroenterol Hepatol* 2004; **19**: 1388-1391
25 **Takahashi H**, Arimura Y, Okahara S, Uchida S, Ishigaki S, Tsukagoshi H, Shinomura Y, Hosokawa M. Risk of perforation during dilation for esophageal strictures after endoscopic resection in patients with early squamous cell carcinoma. *Endoscopy* 2011; **43**: 184-189
26 **Ohki T**, Yamato M, Murakami D, Takagi R, Yang J, Namiki H, Okano T, Takasaki K. Treatment of oesophageal ulcerations using endoscopic transplantation of tissue-engineered autologous oral mucosal epithelial cell sheets in a canine model. *Gut* 2006; **55**: 1704-1710
27 **Saito Y**, Tanaka T, Andoh A, Minematsu H, Hata K, Tsujikawa T, Nitta N, Murata K, Fujiyama Y. Novel biodegradable stents for benign esophageal strictures following endoscopic submucosal dissection. *Dig Dis Sci* 2008; **53**: 330-333

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