Endoscopic Submucosal Dissection of Early Gastric Cancer

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Key Words

Endoscopic submucosal dissection • Early gastric cancer • Indications, gastric cancer • Procedures, gastric cancer • Complications, gastric cancer

Abstract

Endoscopic mucosal resection (EMR) of early gastric cancer (EGC) without any risk of lymph node metastasis was developed in Japan in the 1980s, and it has been one of the standard treatments of EGC for nearly 20 years. Recently, several EMR techniques developed in Japan have been accepted and done in Western countries. These EMR techniques are safe and efficacious but unsuitable for large lesions. Because we could not remove a large lesion in 1 fragment, which was very important for the precise diagnosis of tumor depth, local recurrence increased in large-lesion cases. An innovative procedure using newly developed endoscopic knives, called endoscopic submucosal dissection (ESD), was developed in the late 1990s, which made it possible to remove a large lesion en bloc. Theoretically, ESD has no limitation with respect to tumor size; therefore, it is expected to replace the surgical treatment in some situations. Although ESD has spread throughout Japan within a short period, there remain several disadvantages, such as a higher incidence of complications and a requirement of higher endoscopic skills compared to those of conventional EMR methods. The endoscopic indications, procedures, complications and treatment outcomes of the ESD of EGC are described in this review.

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Introduction

Early gastric cancer (EGC) is defined as a neoplasm confined to the mucosa or submucosa regardless of regional lymph node metastasis [1]. The rate of EGC, which varies by country, is up to 40–60% of all gastric cancer cases in Japan [2–4]. Because the presence of lymph node metastasis has a strong influence on a patient's prognosis, a gastrectomy with complete removal of primary and secondary lymph nodes has been the standard treatment for EGC. The average 5-year survival rate of patients with EGC reached over 90% in Japanese and European data [5–7]. The incidence of lymph node metastasis of EGC is reported as only 3% in intramucosal cases and 20% in submucosal cases [8]. Because of the comparatively lower risk of lymph node metastasis, many EGC surgeries may be excessive treatment. Endoscopic resection is similar to surgery in efficacy but less invasive and more cost-effective. In addition, endoscopic resection allows accurate histological staging of the cancer, which is critical in deciding whether additional treatment is necessary. Thus, endoscopic mucosal resection (EMR) has been widely accepted in Japan as a first-line treatment for EGC without any clinical evidence of lymph node metastasis. EMR is also gaining acceptance in other countries. Recently, an improvement of endoscopic treatment technique and technology resulted in a new EMR method, called endoscopic submucosal dissection (ESD). This article outlines the indications, procedures, complications and treatment outcomes of the ESD of EGC.

Type 0 I		Protruded type
Type 0 IIa		Superficial elevated type
Type 0 IIb		Flat type
Type 0 IIc		Superficial depressed type
Type 0 III		Excavated type

Fig. 1. Macroscopic type of EGC (type 0; superficial, flat tumor with or without minimal elevation or depression).

An Indication for Endoscopic Treatment of EGC

Definition of EGC

EGC is a cancer confined to the mucosa or submucosa (T1 cancer) regardless of regional lymph node metastasis. A macroscopic description, including endoscopic findings, is shown in figure 1. EGC is classified into these types or other complex types, such as IIa + IIc or IIc + III [1]. The aim of the Japanese classification of gastric cancer is to provide a common language for the clinical and pathological description of gastric cancer so as to make a contribution to the research.

Endoscopic Treatment for EGC

Therapeutic endoscopy for gastric cancer plays a major role in various situations. Its indications could be generalized into several categories: (1) to reduce or remove the neoplastic lesion; (2) to palliate the malignant obstruction; (3) to stop tumor bleeding, and (4) other endoscopic palliation. The endoscopic removal of gastric neoplasm is very important for EGC patients without lymph node metastasis and distant metastasis. EMR is a less invasive treatment for EGC that involves the removal of neoplastic lesions without gastrectomy. In addition, EMR provides a method by which we can obtain precise histological findings. Because of this precision, EMR is superior to other endoscopic treatments for EGC, such as microwave coagulation or the injection of anticancer agents. Therefore, EMR has become a common treatment option for EGC patients who have no risk of lymph node metastasis.

Standard Indications for EMR

The indications for EMR are determined by considering the risk of lymph node metastasis, technical problems

such as the size and location of the lesions, the equipment available in the hospitals and the skills of the endoscopists. The standard indication criteria for endoscopic resection of EGC proposed by the Japanese Gastric Cancer Association include: (1) differentiated adenocarcinoma; (2) intramucosal cancer; (3) size of the lesions less than 20 mm; (4) without any endoscopic findings of ulceration [9, 10]. Lesions that meet all of these criteria have little risk of lymph node metastasis and could be removed en bloc by conventional EMR methods.

Extended Indication for EMR

Due to the strict standard criteria for EMR of EGC, many patients have undergone gastrectomy despite a relatively low risk of lymph node metastasis. The extension of the standard criteria for EMR of EGC has been suggested by multiple reports, which revealed the risk of lymph node metastasis in EGC obtained from a large number of surgical cases [10]. The expanded criteria include lesions over 20 mm in diameter and ulcerative lesions that were originally treated by surgical operation.

Technical Transition of the EMR

The endoscopic removal of digestive neoplasms was initially developed as a colorectal polypectomy with a high-frequency electric surgical unit [11]. In Japan, the first description of endoscopic polypectomy as a treatment for pedunculated or semipedunculated EGC was presented in 1974. A revolutionary EMR technique called strip biopsy was reported in 1984 [12]. Strip biopsy was first developed to obtain a larger specimen of gastric mucosa for making a more precise diagnosis; therefore, the name 'biopsy' was derived from the original purpose of the tool. The method of strip biopsy is as follows: (1) a grasper and snare are set in each channel of the double-channel gastroscope; (2) saline is injected into the submucosa under the lesion, and (3) the lesion is lifted with a grasper, while a snare is inserted through the second working channel to remove the lesion. Because this method is technically simple and enhances the ability to make a precise diagnosis from the removed specimen to confirm treatment curability, it has been widely accepted as a treatment for small EGC in Japan despite using a special double-channel gastroscope.

Around the same time, another EMR technique employing a standard endoscopic needle knife called endoscopic resection with local injection of a hypertonic saline epinephrine solution was developed in Japan [13]. In this technique, after the injection of hypertonic saline and diluted epinephrine, the periphery of the lesion is cut with a needle knife. The lesion is then removed using a

Fig. 2. Several endoscopic knives were developed in Japan. They are divided into 2 broad categories as above: tip-covered type and tip-uncovered type. TT knife = triangle-tipped knife.

snare. This technique is more accurate in making the cut margin than other EMR techniques and allows an en bloc resection of the lesion. However, this method has not been so widely accepted thus far because it requires such endoscopic skills as safe usage of the needle knife and the management of bleeding during the procedure.

Several EMR methods using a transparent hood at the end of the endoscope were developed in the early 1990s. EMR by the cap-fitted panendoscope method (EMR-c), which was developed in 1992 for the resection of early esophageal cancer, is smoothly applied to the resection of EGC [14]. First, a special crescent-shaped snare is set inside the cap, and a submucosal injection is made in the lesion. Then the lesion is sucked into the cap while the snare is closed. Thus, the resection of EGC could be safely performed through the submucosal layer under the lesion. This method is performed with a standard endoscope, and therefore this simple procedure is widely used in Japan.

An Innovative Endoscopic Technique: ESD

In Japan, most of the EMR for EGC have been performed by conventional EMR techniques such as strip biopsy or EMR-c. These methods are good for small cancers but are unsuitable for the lesions larger than 20 mm, which is the limit of en bloc resection. Piecemeal resection of the lesion makes it difficult for the pathologist to precisely diagnose and confidently determine the pathological staging. In addition, piecemeal resection leads to

a higher rate of local disease recurrence [15]. Endoscopists have long hoped for the development of a new EMR method that enables the removal of large lesions en bloc, which became a reality in the late 1990s.

A new endoscopic resection technique that included the submucosal cut of lesions with special endoscopic knives was developed in the late 1990s. This method has recently been classified as ESD to distinguish it from conventional EMR. ESD with an insulation-tipped (IT) diathermic knife, which was developed in 1996 at the National Cancer Center Hospital, Tokyo, was the first type of ESD [16, 17]. The IT knife consists of a needle knife and is tipped with a ceramic ball. This knife cuts submucosal layers safely and removes the lesion completely. In Japan, several knives for ESD were developed in the early 2000s at another hospital and have been rapidly and widely spread throughout Japan and several other countries [18–20]. These endoscopic knives for ESD are shown in figure 2.

Procedures

Treatment Technique of Endoscopic Submucosal Resection

ESD with several special endoscopic knives has been developed for removing the EGC en bloc with a standard single-channel endoscope. ESD has made it possible to remove large lesions en bloc, which was impossible with conventional EMR methods.

Standard ESD consists of 3 main steps. First, fluids are injected into the submucosal layer to separate it from the muscular layer. Second, circumferential cuts are made around the lesion. Then, the connective tissue of the submucosa is dissected under the lesion. In this review, we describe the ESD procedure performed using the IT knife.

To accurately remove the lesion, the periphery of the lesion is marked. This marking is usually performed with a standard needle knife. Argon plasma coagulation is also available for peripheral marking. After marking the lesion, the fluid is injected to elevate the lesion and create a space between the submucosal and muscular layers. To promote elevation, several fluids such as saline, glycerol and hyaluronic acid are usually combined with diluted epinephrine, which is used for the prevention of active bleeding.

With a needle knife, a small incision is made to insert the tip of the IT knife into the submucosal layer before starting circumferential mucosal incision. At the periphery of the lesion marking, the mucosa is circumferentially cut with the IT knife. After completion of circumferential incision, an additional diluted epinephrine solution is injected into the submucosal layer to start dissection of the submucosa.

The same IT knife is used to dissect the submucosal layer under the lesion. To prevent gastric perforation, it is important to move the IT knife parallel to the muscular layer. Additional injection of diluted epinephrine solution may be needed to elevate the lesion and obtain a good view of the operation fields. The transparent cap attached at the end of the endoscope provides lesion countertraction, which is similar to a surgeon's left hand, and makes it easy to dissect the submucosal layer. After dissection of the submucosal layer of the lesion, the resected specimen is removed from the body through the mouth.

This ESD technique has made it possible to remove not only large lesions but also lesions with ulcer scars and recurrent tumors after endoscopic resection [21]. Because of severe submucosal fibrosis, these lesions have been too difficult to remove with conventional EMR.

Complications

Bleeding during or after Procedure

There are some disadvantages of ESD with regard to its technical difficulties and complications, such as bleeding and perforation. Bleeding during the procedure sometimes required the procedure to be stopped; how-

ever, with the development of endoscopic technique and technology, we have gradually been able to manage bleeding during the procedure using endoscopic clipping, hot biopsy forceps and others.

Delayed bleeding, which is defined as hematemesis or melena at 0–30 days after the procedure, is treated with emergent endoscopy. The incidence of delayed bleeding after ESD is as common as in conventional EMR, and mostly the bleeding occurs within 12 h after the procedure. The frequency of delayed bleeding differs with the tumor location and size [22, 23].

Perforation during or after Procedure

Compared to conventional EMR, perforation with ESD is higher, and the risk of perforation during ESD is about 1–4%. Perforation has been one of the most dangerous complications and it requires emergency surgical treatment. However, perforation of the stomach is currently managed conservatively without peritoneal dissemination by complete endoscopic enclosure with endoclips [24]. The endoscopic enclosure method has been attempted instead of emergency surgical treatment because the stomach is always clean compared to the full stomach during ESD. A nasogastric suction tube is applied for 12–24 h, and a broad-spectrum antibiotic is given for 48 h. Oral intake is initiated 2–3 days after the procedure, and the patient eventually graduates to normal foods.

Delayed perforation is thought to occur because of the excessive electrical coagulation of the vessels lying within the submucosal or muscular layers. When these vessels need coagulation, care must be taken not to push the device to the gastric wall and not to coagulate for long intervals. If air leakage from the perforated lesion causes severe abdominal fullness, decompression of the pneumoperitoneum must be performed quickly.

Treatment Outcomes

Survival Rate of EGC Treated by Endoscopic Resection

As mentioned above, EMR has become a standard therapy for EGC in Japan because of its successful outcomes. Recently, the long-term outcomes of EMR for small differentiated mucosal EGC of less than 20 mm in size have been reported in comparison to those of surgical treatment [25]. In the report, the disease-specific 5- and 10-year survival rates are both 99%. Now, the treatment outcome of ESD for EGC meeting the expanded criteria are studied in selected centers in Japan.

Table 1. The rate of cut margin free from cancer and 1-piece resection

	<20 mm	20–30 mm	>30 mm	Total
ESD with IT knife	96 (686/785)	91 (187/206)	83 (146/176)	87 (1,019/1,167)
Conventional EMR	45 (172/386)	24 (8/34)	0 (0/10)	42 (180/430)

Figures are percentages with numbers in parentheses. Source: National Cancer Center Hospital and Shizuoka Cancer Center Hospital, 1987–2003 (from Ono [26]).

Recurrence Rate of EGC Treated by Endoscopic Resection

The risk of local recurrence after EMR varies between 2 and 35%, and the recurrence rate correlates with the number of resected specimens. For example, while the recurrence rate stays within 10% when the resected specimens are within 2 pieces, it suddenly rises above 20% when the resected specimens exceed 3 pieces. Some data indicate that single-fragment resection is important with regard to local recurrence [26] (table 1).

Above all the greatest advantage of ESD compared to conventional EMR is the rate of complete resection, which is defined as the cut margin free from cancer and 1-fragment resection. ESD must be able to reduce the risk of local recurrence. However, if the lateral margin of the tumor is misdiagnosed and resected incompletely, local recurrence cases cannot be avoided. Making a precise diagnosis of the tumor is indispensable for initiating ESD.

Future Direction

Further Improvement of the ESD Technique and Technology

Because it achieves a complete resection of EGC and reduces local recurrence, ESD has been widely used throughout Japan despite its technical difficulties. Although ESD still requires endoscopic skills, it is becoming easier and safer because of the development of several new devices (e.g., IT knife 2; Olympus, Japan), special gastroscopes (e.g., the multibending scope; Olympus, Japan) and new electrosurgical units (e.g., VIO 300D; ERBE, Germany) [27]. There will likely be further technological progress in the near future.

Establishing a Suitable Training Program

In Japan, ESD has spread widely within a short period of time [28]. ESD live demonstrations and hands-on seminars have made a contribution to popularizing the ESD

technique and theory. However, there remains the problem of how to control the qualities of the ESD technique between hospitals because there still has been no established training program for ESD. Setting up a suitable training program is imperative.

Extending the Indications

ESD has brought great changes in the endoscopic resection of EGC, and extension of the indication for ESD is expected. In Japan, ESD is clinically indicated for the EGC meeting – not only general criteria for EMR but also extended criteria, which include lesions over 20 mm in diameter and ulcerative lesions. Based on retrospective data, the risk of lymph node metastasis in EGC is thought to be relatively low. Recently, the phase II trial of ESD to expand the indication for EGC (JCOG 0607 study) has been initiated to evaluate the efficacy and safety of ESD for EGC. Through this study, 5-year overall survival, overall survival in cases without ulcerative lesions, overall survival in cases with ulcerative lesions, recurrence-free survival, 5-year recurrence-free survival with stomach, proportion of 1-piece resection, proportion of pathological curative resection after EMR, adverse events and serious adverse events will be assessed.

In the future, further extension of the indication for ESD should be considered. The combination of ESD with laparoscopic lymph node dissection, which has already been reported, might reduce surgery for EGC with risk of lymph node metastasis [29]. Endoscopic full-thickness resection is currently under development in animal models, which has a potential to treat advanced gastric cancer with endoscopy in humans as well [30].

Conclusions

In Japan, endoscopic resection of EGC has become a standard therapy, and it has been gradually accepted in other countries as well. ESD is superior to conventional

EMR in its capability to remove the lesion without size limitation and because it allows complete resection even if the lesion meets the expanded criteria. On the other hand, ESD has several disadvantages. It is a time-consuming procedure, has a higher complication rate of bleeding and perforation, and it requires a high level of endoscopic skill. Although several problems still remain, ESD is one of the best ways for patients suffering from EGC to preserve their stomach and protect their quality of life.

In the field of endoscopy, technological development and theoretical progress will present us an innovative method for the treatment of EGC, which may result in better outcomes.

Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the content of the article.

References

- Japanese Gastric Cancer Association: Japanese Classification of Gastric Carcinoma – 2nd English Edition. *Gastric Cancer* 1998;1: 10–24.
- Everett SM, Axon AT: Early gastric cancer in Europe. *Gut* 1997;41:142–150.
- Nakamura K, Ueyama T, Yao T, Xuan ZX, Ambe K, Adachi Y, et al: Pathology and prognosis of gastric carcinoma: findings in 10,000 patients who underwent primary gastrectomy. *Cancer* 1992;70:1030–1037.
- Shimizu S, Tada M, Kawai K: Early gastric cancer: its surveillance and natural course. *Endoscopy* 1995;27:27–31.
- Okamura T, Tsujitani S, Korenaga D, Hara-guchi M, Baba H, Hiramoto Y, Sugimachi K: Lymphadenectomy for cure in patients with early gastric cancer and lymph node metastasis. *Am J Surg* 1998;155:476–480.
- Sue-Ling HM, Martin IG, Griffith J, Ward DC, Quirke P, Dixon MF, et al: Early gastric cancer: 46 cases treated in one surgical department. *Gut* 1992;33:1318–1322.
- Sasako M, Kinoshita T, Maruyama K: Prognosis of early gastric cancer (with English abstract). *Stomach Intest* 1993;28:139–146.
- Sano T, Kobori O, Muto T: Lymph node metastasis from early gastric cancer: endoscopic resection of tumor. *Br J Surg* 1992;79:241–244.
- Japanese Gastric Cancer Association: Gastric Cancer Treatment Guideline, ed 2 (in Japanese). Kyoto, Japanese Gastric Cancer Association, 2004.
- Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, et al: Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000;3:219–225.
- Deyhle P, Largiader F, Jenny P: A method for endoscopic electroresection of sessile colonic polyps. *Endoscopy* 1973;5:38–40.
- Tada M, Shimada M, Murakami F, Mizumachi M, Arima K, Yanai H, et al: Development of strip-off biopsy (in Japanese with English abstract). *Gastroenterol Endosc* 1984;26: 833–839.
- Hirao M, Masuda K, Asanuma T, Nala H, Noda K, Matsuura K, et al: Endoscopic resection of early gastric cancer with local injection of hypertonic saline-epinephrine. *Gastrointest Endosc* 1998;34:264–269.
- Inoue H, Takeshita K, Hori H, Muraoka Y, Yonesima H, Endo M: Endoscopic mucosal resection with a cap-fitted panendoscope for esophagus, stomach, and colon mucosal lesions. *Gastrointest Endosc* 1993;39:58–62.
- Tada M: One Piece Resection and Piecemeal Resection of Early Gastric Cancer by Strip Biopsy (in Japanese with English abstract). Tokyo, Igaku-Shoin, 1998, pp 68–87.
- Hosokawa K, Yoshida S: Recent advances in endoscopic mucosal resection for early gastric cancer (with English abstract). *Jpn J Cancer Chemother* 1998;25:483.
- Ono H, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, Hosokawa K, Shimoda T, Yoshida S: Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001; 48:225–229.
- Oyama T, Kikuch Y: Aggressive endoscopic mucosal resection in the upper GI tract-hook knife EMR method. *Min Invas Ther Allied Technol* 2002;11:291–295.
- Yahagi N, Fujishiro M, Kakushima N, Iguchi M, Oka M, Kobayashi K, et al: EMR procedure using electro-surgical snare (thin type). *Endos Dig* 2002;14:1741–1746.
- 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;56:507–513.
- Yokoi C, Gotoda T, Oda I, Hamanaka H: Endoscopic submucosal dissection (ESD) allows curative resection of local recurrent early gastric cancer after prior endoscopic mucosal resection. *Gastrointest Endosc* 2006;64:212–218.
- Shiba M, Higuchi K, Kadouchi K, Montani A, Yamamori K, Okazaki H, et al: Risk factors for bleeding after endoscopic mucosal resection. *World J Gastroenterol* 2005;14: 7335–7339.
- Oda I, Gotoda T, Hamanaka H, Eguchi T, Saito Y, Matsuda T, et al: Endoscopic submucosal dissection for early gastric cancer: technical feasibility, operation time and complications from a large consecutive series. *Dig Endosc* 2005;17:54–58.
- Minami S, Gotoda T, Ono H, Oda I, Hamanaka H: Complete endoscopic enclosure using endoclips for gastric perforation during endoscopic resection for early gastric cancer can avoid emergent surgery. *Gastrointest Endosc* 2006;63:596–561.
- Uedo N, Ishii H, Tatsuta M, Ishihara R, Higashino K, Takeuchi Y, et al: Long-term outcomes after endoscopic mucosal resection for early gastric cancer. *Gastric Cancer* 2006; 9:88–92.
- Ono H: Early gastric cancer: diagnosis, pathology, treatment techniques and treatment outcomes. *Eur J Gastroenterol Hepatol* 2006; 18:863–866.
- Isshi K, Tajiri H, Fujisaki J, Mochizuki K, Matsuda K, Nakamura Y, et al: The effectiveness of a new multibending scope for endoscopic mucosal resection. *Endoscopy* 2004; 36:294–297.
- Gotoda T, Friedland S, Hamanaka H, Soetikno R: A learning curve for advanced endoscopic resection. *Gastrointest Endosc* 2005;62:866–867.
- Abe N, Mori T, Takeuchi H, Yoshida T, Ohki A, Ueki H, et al: Laparoscopic lymph node dissection after endoscopic submucosal resection: a novel and minimally invasive approach to treating early-stage gastric cancer. *Am J Surg* 2005;190:496–503.
- Ikeda K, Mosse CA, Park PO, Fritsher-Ravens A, Bergstrom M, Mills T, et al: Endoscopic full-thickness resection: circumferential cutting method. *Gastrointest Endosc* 2006;64:82–89.