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Review

Endoscopic submucosal dissection of early gastric cancer

Takuji Gotoda[1], Hironori Yamamoto[2], and Roy M. Soetikno[3]

[1]Endoscopy Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
[2]Department of Internal Medicine, Division of Gastroenterology, Jichi Medical University, Shimotsuke, Japan
[3]Veterans Affairs Palo Alto Health Care System and Stanford University School of Medicine, Palo Alto, CA, USA

The purpose of this review was to examine a remarkable technical advance regarding the indications for and the technique of endoscopic resection of early gastric cancer. Endoscopic mucosal resection (EMR) of early gastric cancer with no risk of lymph node metastasis has been a standard technique in Japan, probably owing to the high incidence of gastric cancer in Japan and the fact that more than half of Japanese gastric cancer cases are diagnosed at an early stage. Very recently, several EMR techniques have become increasingly accepted and regularly used in Western countries. Although these minimally invasive techniques are safe, convenient, and efficacious, they are unsuitable for large lesions in particular. Difficulty in correctly assessing the depth of tumor invasion and an increase in local recurrence when standard EMR procedures are used have been reported in cases of large lesions, because such lesions are often resected piecemeal owing to the technical limitations of standard EMR. A new development in therapeutic endoscopy, called endoscopic submucosal dissection (ESD), allows the direct dissection of the submucosa, and large lesions can be resected en bloc. ESD is not limited by resection size and is expected to replace surgical resection. However, it is still associated with a higher incidence of complications than standard EMR procedures and requires a high level of endoscopic skill. The endoscopic indications, techniques, and management of complications of ESD for early gastric cancer for properly carrying out established therapeutic endoscopy are described.

Key words: endoscopic submucosal dissection (ESD), early gastric cancer, complications, histological staging

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Reprint requests to: T. Gotoda

Introduction

Therapeutic endoscopy plays a major role in the management of gastric neoplasia. Its indications can be generalized into four broad categories: (1) to remove or obliterate the neoplastic lesion; (2) to palliate malignant obstruction; (3) to treat bleeding, and (4) other (Table 1). Endoscopic removal of gastric neoplasia by resection by means of a high-frequency electric surgical unit or obliteration using laser irradiation, microwave coagulation, or local injection of anticancer agents is performed with the intention to cure. Endoscopic laser irradiation, microwave coagulation, bougienage, and stent placement have been used to palliate malignant obstruction. Endoscopic injection of pure alcohol or hypertonic saline with diluted epinephrine, application of heater probe, argon plasma, or microwave coagulation, and laser irradiation are used to treat bleeding from cancer, with varying degrees of success.

In this review, the specific focus is on endoscopic resection of early gastric cancer (EGC). Endoscopic resection is currently the standard treatment for EGC in Japan.[1] Outside Japan, it is increasingly gaining acceptance.[2,3] Endoscopic resection is similar in efficacy to surgery, minimally invasive, and cheaper to perform.[4] Endoscopic resection allows complete histological staging of the cancer, which is critical because it allows stratification and refinement of further treatment. Endoscopic mucosal resection (EMR) is superior to biopsy for diagnosing superficial gastrointestinal tumors.[5] Other endoscopic techniques may also cure EGC by obliterating it, but they do not provide a pathology specimen.[6]

The status of therapeutic endoscopy for early gastric cancer and, especially, a remarkable technical advance that is expected to supplant EMR, called endoscopic submucosal dissection (ESD), is described in this review.

Table 1. Methodologies of endoscopic treatment for gastric cancer

Cancer reduction
High-frequency electric current: ER, polypectomy
Laser: vaporization, laserthermia, PDT
Microwave coagulation
Injection of anticancer agent
Relief of neoplastic obstruction
Laser vaporization (Nd: YAG, KTP, CO_2, diode, etc.)
Microwave coagulation
Prosthesis for cardiac stenosis
Hemostasis of cancer bleeding
Heater probe
Pure alcohol injection or hypertonic saline epinephrine injection
Microwave coagulation
Low-power laser
High-frequency electric current (coagulation wave)
Other endoscopic palliation
Percutaneous endoscopic gastrotomy (PEG)

ER, endoscopic resection; PDT, photodynamic therapy

Principles of endoscopic resection for EGC

EGC is defined as when tumor invasion is confined to the mucosa or submucosa (T1 cancer), irrespective of the presence of lymph node metastasis.[7] Because the presence of lymph node metastasis has a strong adverse influence on a patient's prognosis,[8,9] gastrectomy with lymph node dissection had been the gold standard for treatment in the past in Japan, even for patients with EGC.[10] Such extensive surgery, however, carries significant risks of morbidity and mortality, and is associated with long-term reduction in the patient's quality of life.[11]

Long-term outcome data from the National Cancer Center Hospital, Tokyo, and others in Japan have shown that the 5-year cancer-specific survival rate for EGC limited to the mucosa is 99%, and that for EGC which has invaded the submucosa it is 96%.[12] In such patients, the incidence of lymph node metastasis of intramucosal cancer is up to approximately 3%. In comparison, the risk increases to about 20% when the cancer involves the submucosa.[13] With stratification, subgroups of patients with EGC who have practically no risk of lymph node metastasis have been identified.[14] Patients with EGC who meet these very specific endoscopic and pathologic criteria are ideal candidates to have their cancer resected through an endoscope.

The major advantage of endoscopic resection is its ability to provide histological staging without precluding future surgical therapy.[15] Larger and deeper endoscopic resection with less diathermic injury is making the histological assessment of depth and margin involvement more reliable.[16] After endoscopic resection, pathological assessment of the depth of cancer invasion, degree of differentiation of the cancer, and lymphatic or vessel involvement allows the risk of lymph node metastasis to be assessed by comparison with published data of patients with similar findings.[17] The risk of developing lymph node metastasis or distant metastasis is then weighed against the risk of surgery.[18] Such precise histological staging, unfortunately, cannot be attained accurately with any imaging technique currently available.[19,20] For example, while endoscopic ultrasound (EUS) is relatively accurate for tumor depth staging, its accuracy is still limited to approximately 80%–90%.[21–23] Thus, final staging should be evaluated only through histological assessment of endoscopically resected material.[24,25]

Indications for endoscopic resection for EGC

Fundamentally, when considering patients' prognoses, those who are stratified into groups with no risk or a low risk of developing lymph node metastasis and with a low-incidence local recurrent disease after resection compared with the risk of mortality from surgery are ideal candidates for endoscopic resection.

Formerly accepted indications for endoscopic resection of EGC include the resection of small intramucosal EGC with intestinal-type histology.[14,26] The rationale for this recommendation was that larger lesions or lesions with diffuse histology may extend into the submucosal layer, and thus the risk of lymph node metastasis is higher. Also, standard EMR methods have the technical limitation that gastric lesions larger than 2 cm in diameter cannot be removed en bloc (Table 2). Therefore, empirical indications for EMR have been (1) papillary or tubular (differentiated) adenocarcinoma, (2) a lesion less than 2 cm in diameter, (3) no ulceration within the tumor, and (4) no lymphatic or vessel involvement.

Clinical observations have shown, however, that the accepted indications for EMR may be too strict and may thus lead to excessive surgery.[27] Therefore, expanded criteria for endoscopic resection have been proposed, because en bloc resection of large tumors is now achievable with the recent development of ESD. The 95% confidence interval (C.I.) calculated from these early studies, however, is too broad for clinical use because of the small sample size.[28–32] More recently, however, by using a large database involving more than 5000 patients who underwent gastrectomy with meticulous R2 level lymph node dissection, Gotoda and colleagues[33] have been able to define the risk of lymph node metastasis in additional groups of patients with EGC with increased certainty (Table 3). These groups of patients have been shown to have no risk or a lower

Table 2. En bloc resection and recurrence rate after various endoscopic resection techniques

EMR			En bloc resection rate (%)			
Author	Year	Methods	≦10 mm	11–20 mm	≧21 mm	Local recurrence rate (%)
Tada	1998	Strip biopsy	70 (421/599)		—	11 (63/599)
Takeshita	1998	EMR-C	80 (44/55)	42 (24/57)	0 (0/9)	1.7 (2/118)
Torii	1999	EAM	84 (52/62)		—	4.8 (3/62)
Hirao	1998	ERHSE	63 (123/196)	44 (60/136)	19 (7/37)	2.3 (8/349)

ESD			En bloc resection rate (%)		
Author	Year		≦20 mm	>21 mm	Local recurrence rate (%)
Ishigooka	2004	ERHSE	—	79 (36/46)	0 (0/46)
Hamanaka	2004	ESD with IT knife	98 (455/463)	96 (235/245)	—
Yahagi	2004	ESD with flex knife	95 (56/59)		—
Yamamoto	2002	EMRSH	100 (37/37)	97 (32/33)	1 (1/70)
Oyama	2004	ESD with hook knife	98 (202/207)	95 (103/109)	—

EMR, endoscopic mucosal resection; EMR-C, EMR with a cap-fitted panendoscope; EAM, endoscopic aspiration mucosectomy; ERHSE, endoscopic resection with local injection of hypertonic saline epinephrine solution; ESD, endoscopic submucosal dissection; IT, insulation-tipped

Table 3. Early gastric cancer with no risk of lymph node metastasis

Criteria	Incidence	95% C.I.
Intramucosal cancer Differentiated adenocarcinoma No lympho-vascular invasion Irrespective of ulcer findings Tumor less than 3 cm in size	0/1230; 0%	0–0.3%
Intramucosal cancer Differentiated adenocarcinoma No lymphovascular invasion Without ulcer findings Irrespective of tumor size	0/929; 0%	0–0.4%
Undifferentiated intramucosal cancer No lymphovascular invasion Without ulcer findings Tumor less than 2 cm in size	0/141; 0%	0–2.6%
Minute submucosal penetration (SM1) Differentiated adenocarcinoma No lymphovascular invasion Tumor less than 3 cm in size	0/145; 0%	0–2.5%

risk of lymph node metastasis compared with the risk of mortality from surgery.

None of 1230 differentiated mucosal gastric cancers less than 3 cm in diameter without lymphatic or vessel involvement or ulceration had lymph node metastases (95% C.I., 0%–0.3%). None of 929 differentiated EGC of any size without lymphatic or vessel involvement or ulceration had nodal metastases (95% C.I., 0%–0.4%). The overall risk of lymph node metastasis in mucosal cancer with diffuse type histology was 4.2%.

However, none of 141 undifferentiated mucosal gastric cancers consisting of poorly differentiated adenocarcinoma or signet-ring cell carcinoma less than 2 cm in diameter without ulceration or lymphatic or vessel involvement had metastasis-positive lymph nodes (95% C.I., 0%–2.6%). The mortality of patients who undergo standard gastrectomy with lymph node dissection at our hospital is up to 0.5%. Considering the surgical mortality and the 5-year survival rate of 99% for mucosal cancer, considerable controversy has been associated with the treatment strategy for patients with mucosal cancer with undifferentiated histology. A recent report involving a large number of patients also has shown that EGC with signet-ring cell carcinoma is associated with a lower rate of lymph node metastasis.[34] This result sug-

gests that mucosal cancer with signet-ring cell carcinoma can also be treated by endoscopic resection.

In submucosally invasive gastric cancer, similar to mucosal cancers, tumor sizes larger than 3 cm with lymphatic or vessel involvement are significantly correlated with an increased risk of lymph node metastases. In addition, cancers penetrating deeply into the submucosal layer are the most likely to be associated with lymph node metastases. Gotoda and colleagues[33] have also shown that none of 145 patients with minute submucosal invasion and a differentiated EGC measuring less than 3 cm, without lymphatic–vascular involvement and with less than 500 μm of submucosal penetration (classified as SM1, minute submucosal invasion, in the Japanese Classification of Gastric Carcinoma) had nodal metastasis (95% C.I., 0%–2.5%). Considering the surgical mortality and 5-year survival rate of 96% in submucosal cancer, surgery may not be necessary for patients with gastric cancer invading the submucosa that fulfills the above conditions.

The results of this study have allowed the expansion of the criteria that candidates for endoscopic resection must meet (Fig. 1).[35] The guidelines for EMR still propose strict criteria because of the technical limitations of endoscopy. However, attempts to expand the indications for ESD to treat EGC are currently underway.

History of endoscopic resection: from the EMR era to the ESD era

Endoscopic cancer removal was initially accompanied by a colorectal polypectomy with a high-frequency electric surgical unit;[36] endoscopic polypectomy to treat pedunculated or semipedunculated EGC in Japan was first described in 1974. By 1984, an EMR technique called strip biopsy was devised as an application of the endoscopic snare polypectomy technique.[37] This method, which uses a double-channel gastroscope, is technically simple and ensures histological assessment of the resected specimen to confirm treatment curability. After submucosal injection of saline under the lesion, the lesion is lifted with a grasper while a snare, inserted through the second working channel, is used to remove the lesion. The method is widely accepted in Japan as a treatment strategy for small EGC.

In 1988, another technique, endoscopic resection with local injection of hypertonic saline epinephrine solution (ERHSE), using a standard endoscopic needle knife, was described for larger lesions and more complete resection.[38] In this technique, after injection of hypertonic saline and diluted epinephrine, the periphery of the lesion is cut with a needle knife. The lesion is then removed by using a snare. This technique allows increased precision to be applied, thus permitting the entire lesion to be removed en bloc. However, although the therapeutic efficacy of this technique is much more reliable than that of strip biopsy, the technique requires considerable skill, as well as the use of a needle knife, which carries a high risk of perforation.

EMR by the cap-fitted panendoscope method (EMR-C; Olympus, Tokyo, Japan), developed in 1992 for the resection of early esophageal cancer, is directly applicable to the resection of EGC.[39] In this technique, a clear plastic cap is connected to the tip of a standard endoscope. Different-sized caps are available according to the diameter of the endoscope and the size of the target lesions.[40] After submucosal injection of the lesion, a special crescent-shaped snare is deployed in the groove at the tip of the cap. The lesion is then suctioned into the cap while the snare is closed. Thus, resection can be safely performed through the submucosal layer under the lesion.[41]

The EMR-L technique (with ligation) uses a standard endoscopic variceal ligation device (Sumitomo Bakelite, Tokyo, Japan) to capture the lesion and make it into a polypoid lesion by deploying the band underneath it.[42] EMR-C and EMR-L have the advantages that they are relatively simple, use a standard endoscope, and do not require an additional assistant. These techniques, however, cannot be used to remove lesions larger than 2 cm en bloc.[43,44] Because piecemeal resections can prevent the pathologist from determining pathological staging with adequate certainty and because there is high risk of recurrence after piecemeal resections,[45] methods to remove large lesions en bloc have been developed.[46]

Endoscopic resection techniques that utilize direct dissection of the submucosa with a modified needle knife have recently been classified as ESD techniques.[47] ESD with an insulation-tipped (IT) diathermic knife, developed at the National Cancer Center Hospital, was the first of these techniques.[48,49] The concept of ESD with an IT knife was initially proposed and modified to make ERHSE, usually performed by a surgeon, easier and safer to perform by an endoscopist. ESD is superior to standard EMR, and an en bloc specimen can be obtained by using a standard single-channel gastroscope. ESD has the advantage of making large en bloc resections possible (Table 2), and it allows precise histological staging and may prevent disease recurrence better than standard EMR methods (Fig. 2). Other endoscopic devices for the ESD procedure, a hook-knife,[50] a flex-knife,[51] and a knife in a small cap technique,[52] have also been described Despite requiring significant additional technical skill and a longer procedure time,[53,54] these ESD techniques are rapidly gaining popularity in Japan, primarily because of the ability to remove large EGC lesions en bloc.

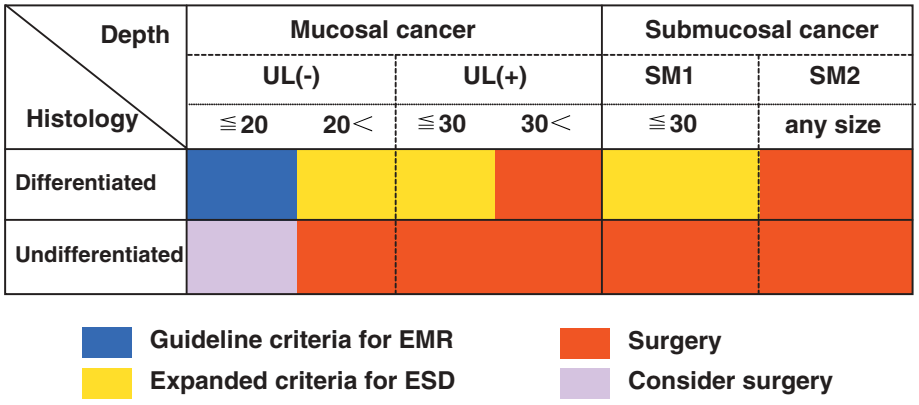

Fig. 1. Guideline criteria for endoscopic mucosal resection (*EMR*) and proposed expanded criteria for endoscopic submucosal dissection (*ESD*). UL, ulceration; SM, submucosal

ESD technique

ESD, which is performed with several special endoscopic knives, has been developed for en bloc resection with a standard single-channel gastroscope (Fig. 3). This promising procedure has the big advantage that en bloc resections of large lesions are achievable. In this review, we describe in particular the established ESD technique for en bloc resection and comment on the set-up of the high-frequency electric surgical unit (Table 4).

ESD consists of three steps: injecting fluid into the submucosal layer to separate it from the muscle layer, circumferential cutting of the mucosa surrounding the lesion, and submucosal dissection of the connective tissue of the submucosa under the lesion.[55]

Marking of the periphery of the lesion (Fig. 4A–C) is begun by using a standard needle knife (or a hook, flex, triangle-tipped, or flash knife) with a forced 20 W coagulation current (ICC200, Erbe, Tubingen, Germany). After injection of diluted epinephrine (1:100 000) to raise the submucosal layer, a small initial incision (Fig. 4D) is made with a standard needle knife in the 80-W endocut mode with effect 3 (ICC200, Erbe) for insertion of the tip of the IT knife into the submucosal layer.

Then circumferential mucosal cutting at the periphery of the marking dots (Fig. 4E–G) is performed with an IT knife in 80-W endocut mode. The ceramic ball prevents perforation of the muscle layer. After completion of the circumferential cutting, diluted epinephrine is injected submucosally (Fig. 4H).

With the same IT knife, the submucosal layer under the lesion is directly dissected (Fig. 4I) using a lateral movement. It is important to cut tangentially to the submucosal layer to avoid perforation. Diluted epinephrine can be injected into the submucosa at any time to raise and confirm the submucosal layer. A cap attachment (Olympus) is frequently useful for creating countertraction, making it easier to exfoliate the submucosal tissue (Fig. 4J). Complete endoscopic submucosal dissection can achieve a large one-piece resection without size limitation (Fig. 4K). Finally, the resected specimen is retrieved with grasping forceps.

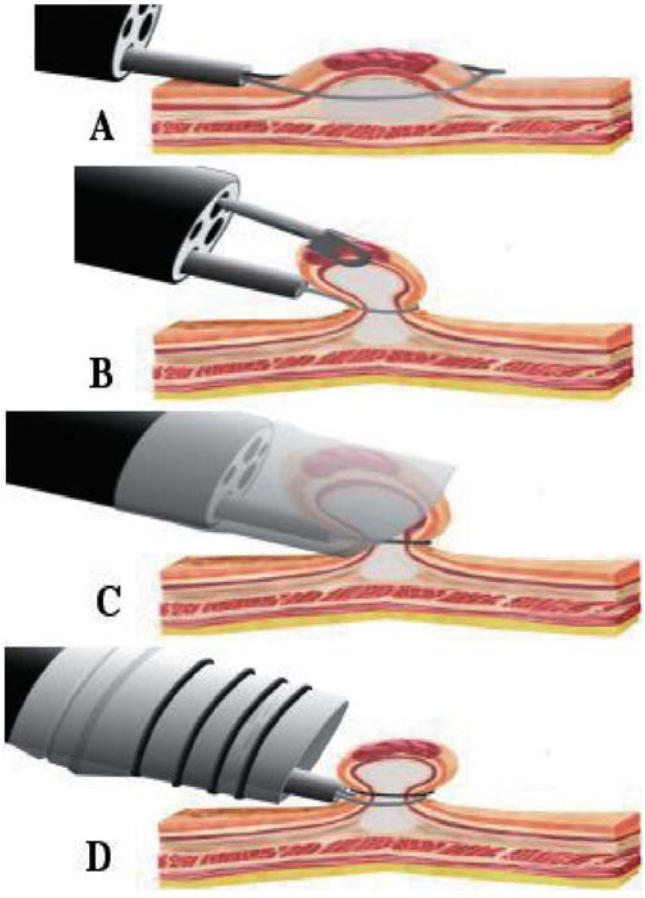

Fig. 2A–D. Standard EMR methods. **A** Snare polypectomy; **B** strip biopsy; **C** EMR with cap technique; **D** EMR with ligation technique

This procedure allows the removal of ulcerated gastric lesions and resection of recurrent EGC after EMR. Previously, it was difficult, if not impossible, to resect

Fig. 3A–I. Endoscopic devices for ESD. **A** Insulation-tipped (IT) knife (KD-610L, Olympus); **B** modified IT knife with three-pointed star blade (Olympus); **C** needle knife (KD-1L-1, Olympus); **D** hook knife (KD-620LR, Olympus); **E** flex knife (KD-630L, Olympus); **F** triangle-tipped knife (Olympus); **G** flash knives with several lengths of needle (Fujinon Toshiba ES systems); **H** Mucosectom (DP-2518, PENTAX); **I** small-caliber tip (ST) with transparent hood (DH-15GR, 15CR, Fujinon Toshiba ES systems)

these lesions by conventional ER techniques because submucosal fibrosis prevented adequate lifting of the mucosal lesion by submucosal injection.[56]

Histological staging

The retrieved ESD specimen is flattened and fixed (Fig. 4L). Additional resections and reconstructions are seldom necessary because the marking dots are completely included in the en bloc resection. Accurate evaluation is possible only when the specimen is oriented immediately after it is removed from the endoscopy unit, before it is immersed in formaldehyde. Orientation of the specimen is accomplished by fixing its periphery with thin needles inserted into an underlying plate of rubber or wood. The submucosa side of the specimen is apposed to the plate.

After fixation, the specimen is sectioned serially at 2-mm intervals parallel to a line that includes the closest resection margin of the specimen so that both lateral and vertical margins are assessed. The depth of tumor

Table 4. Set-up of high-frequency electric surgical unit (ICC200, ERBE)

		Cutting and dissection			Cagulation	
Procedure	Device	Mode	Effect	Output	Mode	Output
Marking	Needle knife				Forced/soft	20/40
	Hook knife				Soft	40
	Flex knife	Endocut	3	80	Soft	50
Precutting	Needle knife	Endocut	3	80		
Mucosal cutting	IT knife	Endocut	3	80–120		
	Needle knife	Endocut	3	80–120		
	Flex knife	Endocut	3	120		
	Hook knife	Endocut	2	80		
Submucosal dissection	IT knife	Endocut	3	80	Forced	50
	Needle knife	Endocut	3	80	Forced	25 or 50
	Hook knife				Forced	60
	Flex knife				Forced	40 or 60
Endoscopic hemostasis	IT knife				Forced	50
	Needle knife				Spray/forced/APC	25/50/20
	Hook knife				Spray	60
	Flex knife				Forced	40
	APC				Spray	40
	Monopolar forceps				Soft	60 or 80
	Bipolar forceps				Bipolar	30

APC, argon plasma coagulation

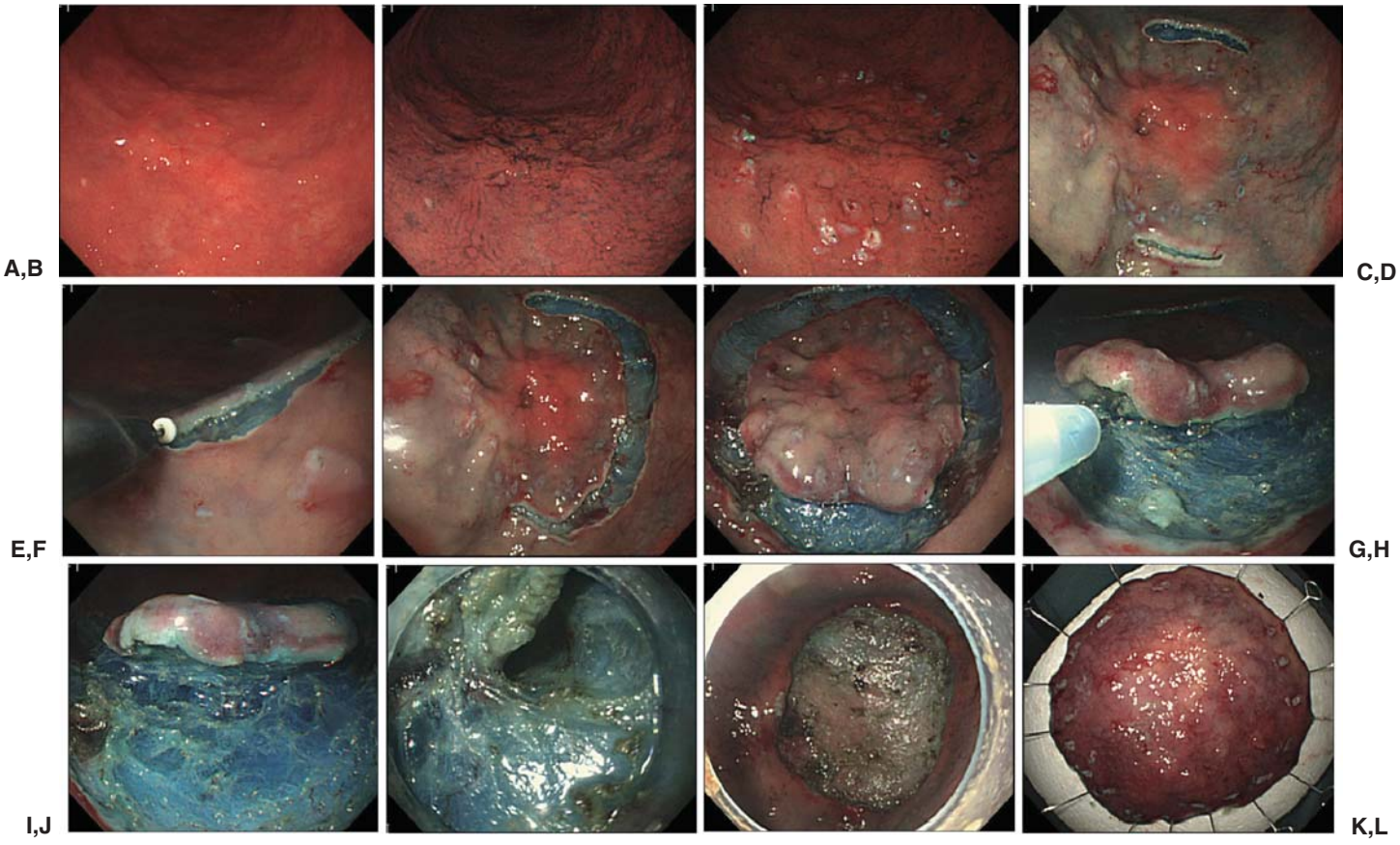

Fig. 4A–L. ESD procedures. **A** Locally recurrent tumor on greater curvature of gastric antrum after insufficient EMR; **B** indigo carmine dye spray for deciding tumor border; **C** markings by needle knife with coagulation current; **D** making small initial incision with a needle knife in endocut mode after injection of diluted epinephrine; **E** ceramic ball preventing perforation of the muscle layer; **F** mucosal cutting with an IT knife in endocut mode; **G** circumferential mucosal cutting at the periphery of the marking dots; **H** additional submucosal injection of diluted epinephrine after completing the circumferential cutting; **I** dissecting the submucosal layer with an IT knife in ENDO CUT mode; **J** cap attachment for stretching the submucosal tissue; **K** large ESD defect after complete one-piece resection without perforation; **L** ESD specimen on a plate with its periphery flattened by thin needles

Table 5. Bleeding and perforation rate of endoscopic resection

	Author	Method	Total cases	Bleeding (%)	Perforation (%)
EMR	Torii	EAM	24	8.3	4
	Tada	Strip biopsy	599	1.3	0.2
	Chonan	EMR-C/strip biopsy	123	7	4
	Takeshita	EMR-C	121	14.9	0
	Tanabe	EAM	206	13	1.5
	Ohkuwa	Strip biopsy	88	4	1
	Ono	Strip biopsy/(IT-ESD)	479	—	5
ESD	Hirao	ERHSE	373	6.7	2.9
	Ohkuwa	ESD with IT knife	41	22	5
	Miyamoto	ESD with IT knife	123	38	0
	Oda	ESD with IT knife	1033	6	4
	Yamamoto	EMRSH	70	4	0
	Yahagi	ESD with flex knife	59	1.7	3.4

EMRSH, EMR with circumferential mucosal incision assisted by submucosal injection of sodium hyaluronate

invasion (T) is then evaluated along with the degree of differentiation and lymphatic or vascular involvement. Because, at present, the abovementioned factors related to lymph node metastasis are diagnosed only through histological assessment, it is impossible to return a definite diagnosis regarding tumor depth, histological type, and lymphatic vessel invasion before treatment. It is difficult to overemphasize the importance of meticulous histological staging after endoscopic resection. Large en bloc resections not only avoid locally recurrent disease but also enable precise and complete histological staging.

Pathological reports of resected specimens must include histological type and tumor depth, size, location, and macroscopic appearance. The presence of ulceration or lymphatic and venous involvement, if any, and the status of the margin of the resection should be reported in detail to determine curability. If the specimen is insufficient, tumor staging cannot be accurately assessed, a patient's prognosis cannot be estimated, and potential needs for additional therapy, which may be curative, cannot be assessed.[57,58]

Management of complications during ESD and clinical course after ESD

The complications of endoscopic resection for EGC include pain, bleeding, and perforation (Table 5). Pain after resection is typically mild.[59] The standard dose of proton-pump inhibitor is administered for 8 weeks to prevent postoperative bleeding and promote ulcer healing, and patients are typically placed on nothing per mouth for 1 day,[60] followed by clear liquid on the second day, and a soft diet for another 3 days. Large ulcers after ESD have recently been reported to heal within 8 weeks after resection under antacid treatment.[61–63]

Table 6. Relations between delayed bleeding and tumor location, size, and ulcer finding

		Delayed bleeding	*P* value
Location	Upper third	1% (1/176)	
	Middle third	6% (24/431)	0.001
	Lower third	6% (31/426)	<0.001
Size (mm)	⩽20	5% (35/719)	
	21–30	7% (13/176)	0.184
	⩾31	8% (11/138)	0.139
Ulcer finding	Positive	5% (13/243)	
	Negative	6% (46/790)	0.781

Bleeding is the most common complication, occurring in up to 8% of patients undergoing standard EMR and in up to 7% of patients undergoing ESD[64,65] (Table 6).

Immediate bleeding, which can be brisk, appears more common with resections of tumors located in the upper third of the stomach. During ESD, immediate minor bleeding is not uncommon but can be successfully treated by grasping the bleeding vessels with hot biopsy forceps and coagulating them with the 80-W soft coagulation mode of the ICC 200 (Fig. 5A, B).[66] Endoclips are also often deployed for more brisk bleeding. Delayed bleeding, manifested by hematemesis or melena at 0–30 days after the procedure, is treated by emergent endoscopy, performed after fluid resuscitation, using similar techniques.[67] Delayed bleeding is common after ESD, but most bleeding (75%) occurs within 12 h after the procedure and is also strongly related to tumor location and size.[68]

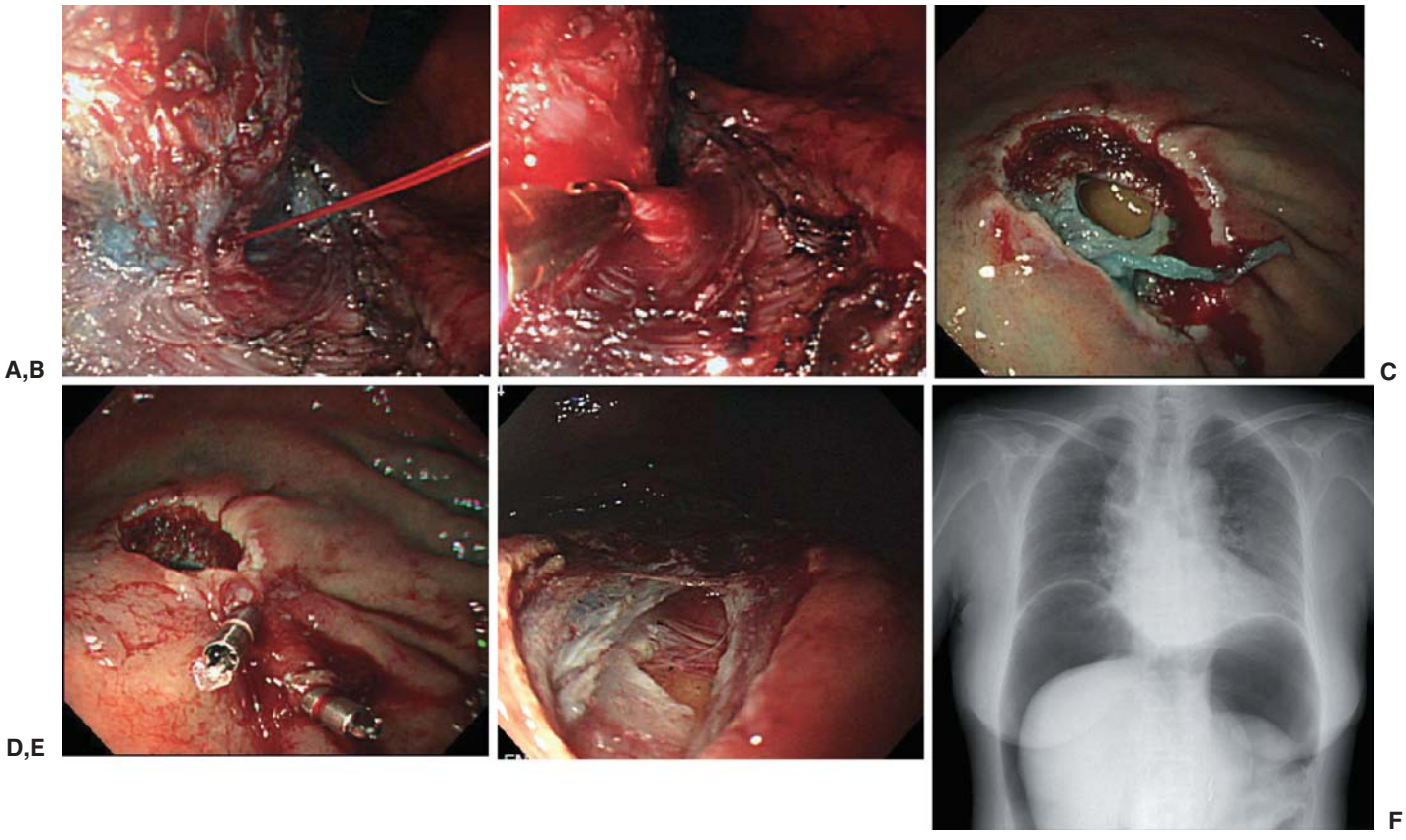

Fig. 5A–F. Complications during ESD and management. **A** Arterial bleeding from an exfoliated submucosal layer; **B** endoscopic capture and hemostasis of the bleeding vessel; **C** perforation on the greater curvature of the upper body; **D** endoscopic closure with endoclips; **E** small perforation; **F** pneumoperitoneum

Table 7. Relations between perforation and tumor location, size, and ulcer finding

		Perforation	*P* value
Location	Upper third	7% (13/176)	<0.001
	Middle third	4% (16/431)	<0.05
	Lower third	1% (6/426)	
Size (mm)	⩽20	3% (18/719)	
	21–30	3% (6/176)	0.184
	⩾31	8% (11/138)	0.139
Ulcer finding	Positive	6% (14/243)	<0.05
	Negative	3% (21/790)	

Perforation is uncommon with EMR but is seen relatively more often with ESD. The risk of perforation during ESD is about 4%. Perforation is related to tumor location and ulcer findings but not tumor size (Table 7). Perforations are typically closed with endoclips (HX-600-090; Olympus) without peritoneal dissemination.[69,70] When gastric perforation occurs during endoscopic resection for EGC, surgical treatment has been generally performed. However, gastric perforation during endoscopic resection can be conservatively treated by complete endoscopic closure with endoclips. Nasogastric suction is applied for 12 h, and broad-spectrum antibiotic is given for 2 days. A soft meal diet is advanced 3 or 4 days later, and most patients are discharged within 7 days. Endoscopic closure of gastric perforation with endoclips has been attempted because the stomach of these patients is thought to be comparatively clean during ESD because the patients fast before undergoing the procedure and because of the antibacterial effect of gastric acid (Fig. 5C, D). Vital signs such as blood pressure, oxygen saturation, and electrocardiograms must be checked during endoscopic procedures. If abdominal fullness due to air leakage from the perforated lesion is severe (Fig. 5E, F), decompression of the pneumoperitoneum must be performed by using a 14G puncture needle with side slits after testing with a 23G needle syringe filled with saline with confirmation by transabdominal ultrasonography.

Recently, to prevent gastric perforation, polyethylene glycol or sodium hyaluronate as an injection agent have

been reported to make the ESD procedure easier and safer, as these agents stay longer in the submucosa and produce a clearer dissection layer.[71,72] Both the tissue damage caused by the injection solution and its lesion-lifting ability should be considered for accurate histological assessment. A solution of hyaluronic acid combined with glycerin is the most favorable submucosal injection solution for minimizing tissue damage and providing sufficient lesion-lifting ability.[73]

Outcomes of endoscopic resection, problems to be solved, and future prospects

Successful outcomes have led to EMR becoming the standard treatment for EGC in Japan.[74] Kojima and colleagues[75] review the outcomes of EMR at 12 major institutions in Japan. Recently, 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. Reported disease-specific 5- and 10-year survival rates are both 99%.[76] In selected centers in Japan, the long-term outcomes for patients treated by ESD on the basis of the expanded criteria are currently being studied. The incidence of multiple metachronous gastric cancer (MGC) in patients who have undergone endoscopic resection for the initial lesion should be prospectively investigated to ensure sufficient follow-up surveillance endoscopy.[77] A recent study has shown that the average time to detect a first MGC is 3.1 ± 1.7 years after EMR, and the cumulative 3-year incidence is 5.9%.[78] An annual endoscopic surveillance program is both practical and effective for patients who have undergone endoscopic resection, and should be sufficient for early detection of multiple MGC as well as the first one.

As previously mentioned, however, standard EMR techniques are associated with a risk of recurrence, especially when the resection is not en bloc or when the margins are not clear. The risk of local recurrence after EMR varies between 2% and 35%. ESD is still being developed and requires a high level of skill on the part of the endoscopist even nowadays.[79] Global use of the ESD technique has the potential to cure many patients with EGC. The significant learning curve associated with achieving proficiency in these resections reflects the experience that is necessary to acquire the skills to perform this technique safely and effectively.

Endoscopic resection should be safe, effective, and applicable in a wide variety of clinical situations. In fact, rapid technical progress such as the development of the ESD procedure has brought about great changes in endoscopic resection for EGC. Although several endoscopic devices have been developed for making ESD easier and safer,[80] this technique still requires an experienced endoscopist with a high level of skill because the procedures have to be performed through only one gastroscope, thus requiring one-handed surgery. Recently, procedures using countertraction of lesions during gastric ESD have been studied. Percutaneous traction-assisted EMR has been developed to apply strong countertraction.[81] We are now planning a clinical trial of magnetic-assisted ESD, which involves an clip attached with an anchor to the lesion and controlled magnetically outside of the patient to apply strong countertraction.[82]

To further expand the indications for treating EGC with less invasive surgery, resection that combines ESD with laparoscopic regional lymph node dissection should be considered.[83,84] The combination of ESD and laparoscopic lymph node dissection might reduce surgery for EGC cases at risk for lymph node metastasis. Endoscopic full-thickness resection, which is under development in animal studies, will allow a more complete histological examination of the gastrointestinal cancer.[85]

There may be many indications for ESD in Western countries, where ESD might have a much higher therapeutic impact than in Japan because of the higher surgical mortality in the West.[86] Endoscopic resection has been generally uncommon in the West because of the very low incidence of small EGC there, in contrast to the higher incidence of EGC in Japan.[87] Considering the incidence of colorectal cancer or Barrett's cancer in the West, the technological advance of ESD promises additional applications in cancer treatment, including for colorectal and esophageal tumors.[88]

The low incidence of EGC in Western countries may be explained by the different histological criteria used between the West and Japan (Fig. 6); most intestinal-type mucosal cancers in Japan are not regarded as cancer in the West.[89] There are large discrepancies between Western and Japanese pathological diagnoses, and these differences in diagnostic criteria have caused considerable problems in the interpretation of Japanese cancer research by Western clinicians and researchers. Carcinoma is defined as invasion of the submucosal layer, muscularis mucosa, or at least the lamina propria in the West. In Japan, cellular and structural atypia, regardless of whether invasive findings are present, are used to diagnose a gastrointestinal neoplasm. Whichever is more correct, such lesions are to be diagnosed as being neoplastic or dysplastic histologically and may be an indication for endoscopic resection regardless of their size, according to the Vienna classification (Table 8).[90] To avoid further confusion concerning the terms adenoma, dysplasia, and carcinoma, use of a consensus classification such as the Vienna classification should be considered.

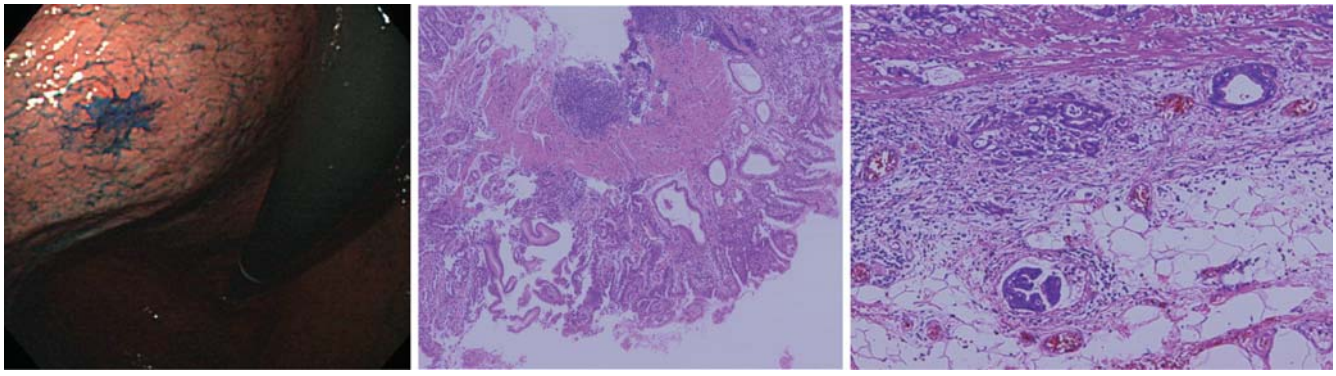

Fig. 6A–C. Histological diagnosis of early gastric cancer. **A** Small depressed lesion on the posterior wall of the upper gastric body; **B** no invasive finding, classified as dysplasia (Vienna classification 4.1.) in the West but diagnosed as well-differentiated adenocarcinoma (Vienna classification 4.2.) in Japan on biopsy sample; **C** submucosally invasive adenocarcinoma with lymphatic involvement (Vienna classification 5.2.) in resected specimen

Table 8. Vienna classification

Category	Definition	Treatment
1.	Negative for neoplasia/dysplasia	No treatment
2.	Indefinite for neoplasia/dysplasia	Follow-up, recheck
3.	Noninvasive low-grade neoplasis	Follow-up
4.	Noninvasive high-grade neoplasia	Endoscopic resection, surgery
4.1.	High-grade adenoma/dysplasia	
4.2.	Noninvasive carcinoma (CIS)	
4.3.	Suspicious of invasive carcinoma	
5.	Invasive neoplasia	Surgery (recently ESD)
5.1.	Intramucosal carcinoma	
5.2.	Submucosal carcinoma or beyond	

CIS, cancer in situ; Intramucosal, invasion into the lamina propria or muscularis mucosa

Conclusions

Endoscopic resection of EGC is now standard therapy in Japan, and it is increasingly becoming accepted and regularly used in other countries. The techniques, indications, and histological staging in the treatment of EGC are described. The great advantages of ESD over standard EMR methods are that the resected size and shape can be endoscopically controlled, en bloc resection is possible even with large tumors, and tumors with ulcers can be resected. On the other hand, ESD has the following disadvantages: the procedure takes a long time, there is a higher complication rate of bleeding and perforation, and it involves endoscopic techniques requiring a high skill level. A suitable training program is now required for this technique to become widely used. Ideally, continued progress in the therapeutic endoscopic field will lead to more outcomes, research, and simplified techniques.

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