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Endoscopic Submucosal Dissection of Early Gastric Cancer and Gastric Tumors

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Abstract

Endoscopic submucosal dissection (ESD) is a new endoscopic resection technique introduced after endoscopic mucosal resection (EMR) by which the endoscopist can remove a superficial gastrointestinal neoplasm. The endoscopist can determine the incision line preoperatively and can resect even relatively large mucosal tumors en bloc using the ESD technique. ESD has four steps: marking around the lesion, submucosal injection, circumferential incision of the mucosa, and finally dissection of the submucosal layer. ESD requires specific endosurgical knives that are divided into two basic types, the tip-covered type and the tip-noncovered type. The drawbacks of ESD are that it is more time consuming and has a higher rate of complications (bleeding and perforation) compared with EMR. These problems are being overcome gradually with advances in devices and endoscopist skill. The indication for ESD has been extended to not only gastric neoplasia but also esophageal and colonorectal neoplasia.

In 1984, Tada et al. [1] developed endoscopic mucosal resection (EMR), by which the endoscopist could remove a superficial gastrointestinal neoplasm using a two-channel scope with grasper forceps and a snare after local injection of solution into the submucosa, and which can be used to treat flat or even depressed lesions. About 15 years later, a new endoscopic resection technique, endoscopic submucosal dissection (ESD), was invented in Japan. ESD evolved from one of the EMR techniques, ERHSE (endoscopic resection after local injection of a solution of hypertonic saline-epinephrine invented by Hirao et al. [2]). In the late 1990s, Hosokawa and Yoshida [3] and Ono et al. [4] started the development of the IT knife (insulation-tipped diathermic knife) at the National Cancer Center. This is an epoch-making device in the field of endoscopic resection. EMR is a very convenient method for the resection of gastrointestinal tract mucosal tumors in a short operating time. However, it has two drawbacks, namely limited size of resectable tumor and inability of the endoscopist to decide the incision line preoperatively. These have led to a slightly high recurrence rate of resected tumors. With the advent of ESD, the endoscopist can choose the incision line preoperatively and can resect even relatively large mucosal tumors en bloc. In this chapter we will introduce the technique of ESD.

Technique

Figure 1 shows the ESD procedure. The lesion is a IIc type early gastric cancer on the lesser curvature of the antrum. First is marking and injection of solution into the submucosa, followed by circumferential mucosal incision, submucosal dissection, resection, and comparison between pretreatment findings and the resected specimen.

Figure 2 shows the ESD knives. These endosurgical knives are divided into two basic types, the tip-covered type and the tip-noncovered type [5]. These originated from the conventional needle knife. The IT knife (KD-610L, Olympus) is a tip-covered knife. In the tip-noncovered group of endosurgical knives, the hook knife (KD-620 LR, Olympus) was developed by Oyama and Kikuchi [6], the flex knife (KD-630L, Olympus) by Yahagi et al. [7], the triangle-tipped knife by Inoue and Kudo [8], and the FlushKnife (DK2618JN10-30, Fujinon) by Toyonaga et al. [9]. In 2003, the new name *endoscopic submucosal dissection,* ESD, was proposed for this technique that is able to resect completely the superficial neoplasm that was impossible to resect en bloc by EMR. In general, the IT knife is most applicable to gastric tumors and tip-noncovered types for the esophagus or colorectum. In difficult cases, even for gastric neoplasms, a combination of two or three ESD knives is recommended.

ESD is supported by several advances in endoscopic equipment and medical support devices. In addition to endosurgical knives, ESD requires a specific endoscope with water jet and high-frequency generators. The endoscope for ESD is required to have a water jet system because the operator always encounters bleeding during the ESD procedure and needs to stop it immediately. In Japan, the GIF Q260-J (Olympus) high-frequency generator is most commonly used; the ICC 200 or VIO 300 D (ERBE GmbH, Tübingen, Germany) is also essential for ESD because they provide an endo-cut mode, a dry-cut mode, and multiple coagulation modes that are useful for ESD. These high-frequency generators can control the bleeding of a mucosal incision or submucosal dissection easily. Against bleeding of larger vessels in the submucosal layer, we should use hot biopsy or a Coagrasper (FD-410LR, Olympus) with soft coagulation mode.

Indications

The most important point for application of ESD is to detect an early gastric cancer. The endoscopist should obtain a good visual filed while doing esophagoduodenoscopy. Usually the patient is administered 20,000 units of pronase and 1g of sodium hydrogen carbonate as oral premedication to decrease gastric juice and reduce bubbles before examination. If the endoscopist finds bubbles or mucus that disturb the endoscopic view even after such premedications, s/he should wash the unclear area with water containing bubble-reducing agents. To detect early gastric cancer, s/he should take into careful consideration minute changes in the color or surface appearance of the gastric mucosa. Sometimes spraying of indigo carmine can help the endoscopist detect early gastric cancer.

Before ESD, it is important to investigate the histology, the depth, and the lateral margin of the tumor. The indications for conventional EMR are mucosal cancer, differentiated adenocarcinoma, with no ulcer or ulcer scar and <2 cm in diameter. Recently, extended indications for endoscopic resection of early gastric cancer would be necessary because the above criteria are very strict and ESD is able to remove larger tumors compared with conventional EMR. Table 1 shows the indications for conventional EMR and for ESD for early gastric cancer [10, 11]. Since

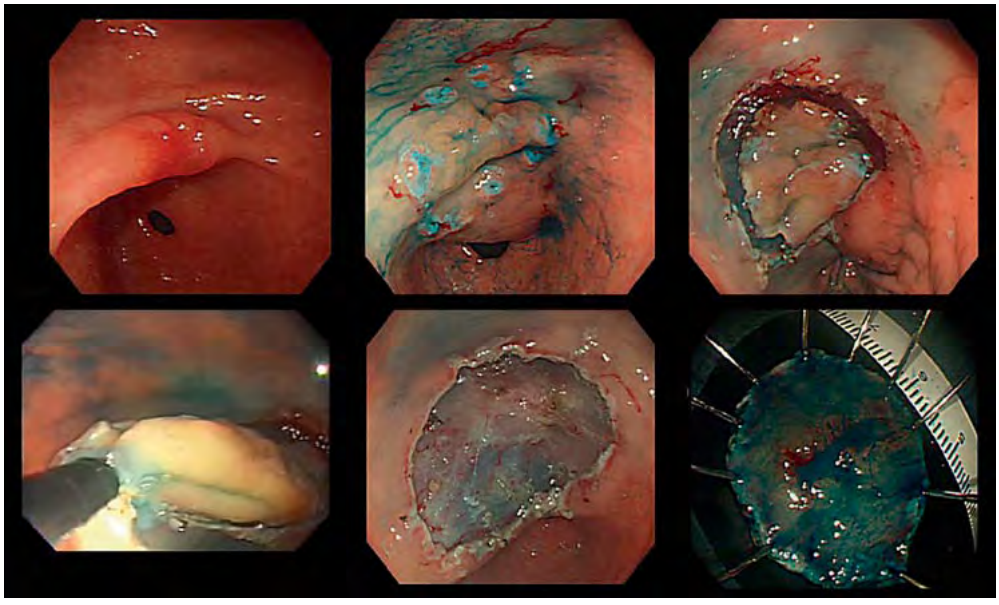

Fig. 1. The ESD procedure. The lesion is a IIc type early gastric cancer on the lesser curvature of the antrum. First is marking and injection of solution into the submucosa, followed by circumferential mucosal incision, submucosal dissection, resection, and comparison between pretreatment findings and the resected specimen.

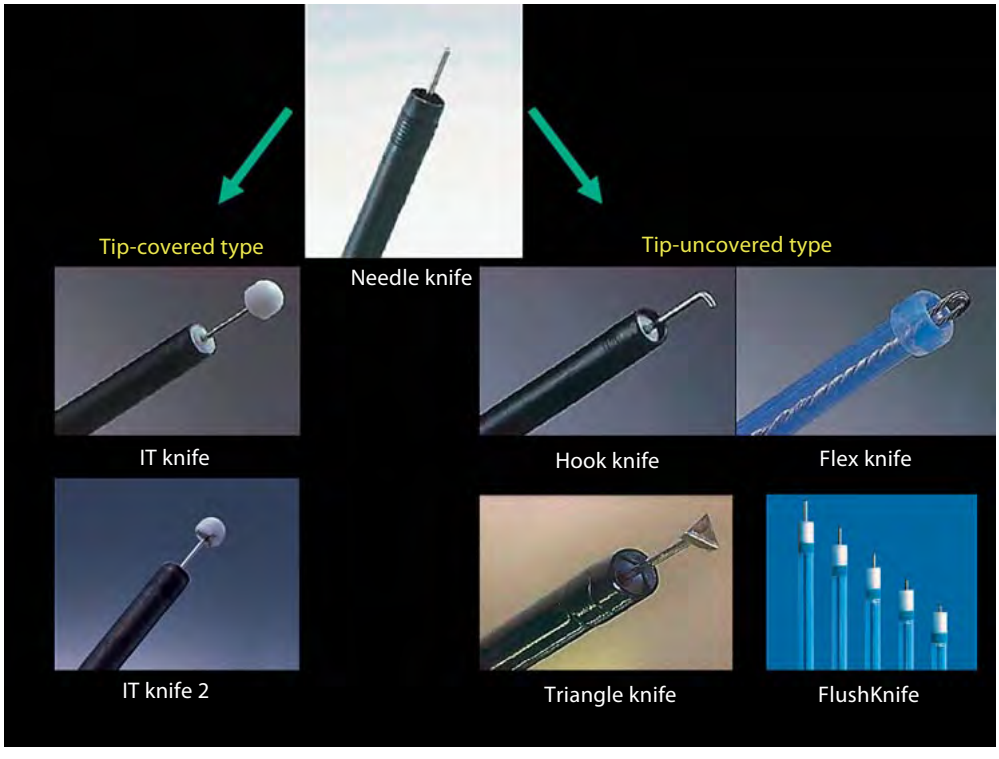

Fig. 2. The ESD knives. These endosurgical knives are divided into two basic types, the tip-covered type and the tip-noncovered type.

Table 1. Indications of EMR or ESD for early gastric cancer

Depth and histology	Mucosal cancer				Submucosal cancer	
	UL(–)		UL(+)		SM1	SM2
	≦20	<20	≦30	<30	≦30	any size
Differentiated	A	B	B	D	B	D
Undifferentiated	C	D	D	D	D	D

A = Guideline criteria for EMR, B = expanded criteria for ESD, C = consider surgery, D = surgery.

ESD enables en bloc resection of larger tumor compared with conventional EMR, we need the new criteria for the indications of early gastric cancer. Gotoda et al. [10, 11] reported that the criterion of lymph node-negative gastric cancer has been defined from a large database of over 5,000 patients with early gastric cancer who underwent gastrectomy with D2 lymph node dissection. According to their papers, differentiated type intramucosal carcinoma without ulcer findings and <3 cm in diameter differentiated type intramucosal carcinoma with ulcer findings do not show lymph node metastasis. Undifferentiated type intramucosal carcinoma is controversial for ESD because the margin of the tumor is not so clear due to its invasive behavior. We recommend endosonography before ESD in addition to abdominal CT. Endosonography shows the layer of the gastric wall so clearly that the submucosal invasion or ulcerated change is recognized objectively.

General Procedure of ESD

Patient position for ESD is the same as for diagnostic esophagoduodenoscopy, the left lateral position. Usually the patient is given a venous infusion and administered a sedative and analgesic. When the operation time is expected to be over several hours, general anesthesia may be recommended.

In general, ESD has four processes: marking around the lesion, submucosal injection, circumferential incision of the mucosa, and finally dissection of the submucosal layer. When we perform ESD, after insertion of the endoscope, we insert an overtube for endoscopic variceal ligation (Sumitomo Bakelite Co. Ltd, Tokyo, Japan) to insert or extract the endoscope smoothly. During ESD in the submucosal layer, since the lens is sometimes clouded with gastric juice, blood, and fat, we have to clean the lens of the endoscope. When we insert a scope with attachment or change endoscopes, the overtube is useful and results in less damage to the patient (fig. 3).

Step 1: Marking

When making marks around the lesion, we use a needle knife. To avoid perforation, we keep in mind the length of the protruded needle. If an endoscopist feels unsettled about needle movement, s/he should put a transparent attachment on the distal tip of the endoscope from the first marking session. This attachment helps the endoscopist keep a constant and stable

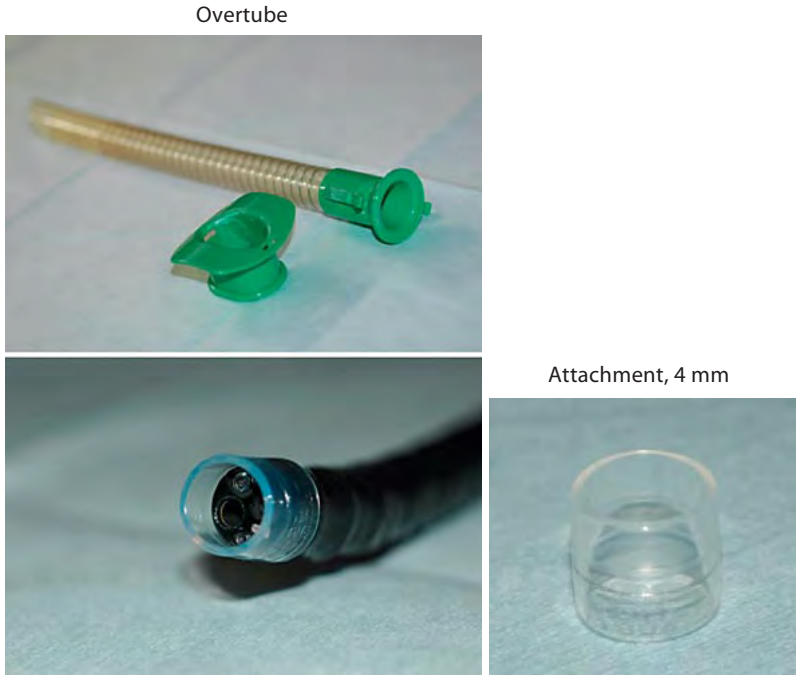

Fig. 3. Upper: An overtube for endoscopic variceal ligation (Sumitomo Bakelite Co. Ltd, Tokyo, Japan). Bottom: An attachment (Olympus, D-201-11804).

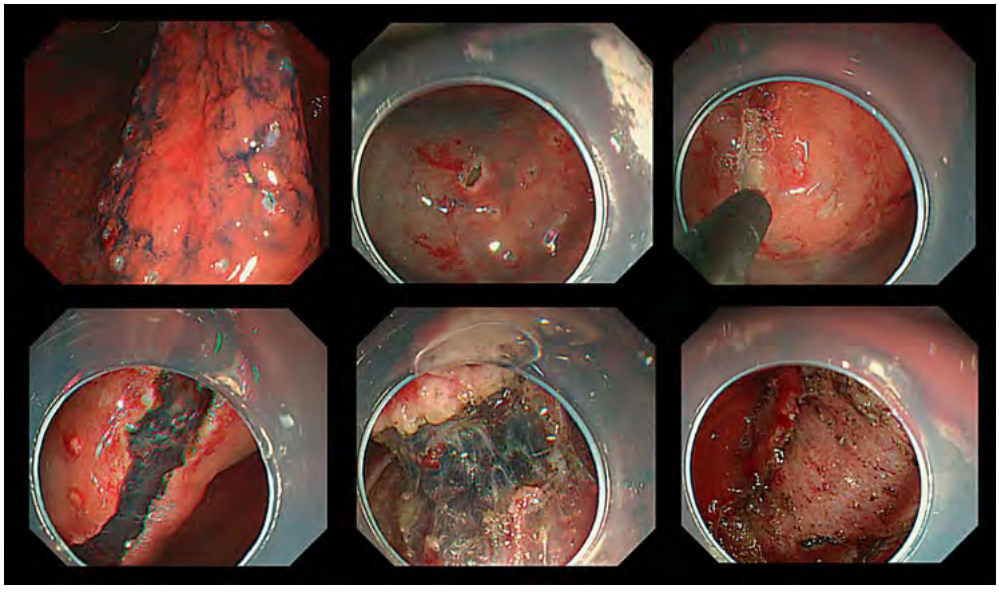

Fig. 4. When the endoscopist injects solution into the submucosa, s/he should keep in mind the position of the first mucosal incision. The endoscopist makes a small hole with a conventional needle knife or tip-non-covered type. Then the operator puts the IT knife into the hole. The IT knife should be used in a drawing manner, from the distal point to the proximal point; visually from the standard point of the angulus, the endoscopist makes the first incision at a point distal from. After the circumferential mucosal incision, the operator should start the submucosal dissection. Following the injection of solution into the submucosa, s/he starts dissecting from the right to the left or in the reverse direction in the submucosa.

distance between the tip of the endoscope and the mucosa. If the patient is prone to easy bleeding, for example, has liver cirrhosis or renal dysfunction, we could choose APC in marking for the gastric body lesions.

Step 2: Submucosal Injection

When the endoscopist injects solution into the submucosa, s/he should keep in mind the position of the first mucosal incision (fig. 4). Usually we add indigo carmine to the injection solution, for example saline, glycerol, or hyaluronic acid. When the endoscopist treats a lesion in the gastric body, hyaluronic acid should be selected because its duration in the submucosal layer is long and helps to avoid perforation [12]. If the operator injects continually, s/he should put the solution into the elevated area. If s/he puts the solution into the flat area, the risk of bleeding might increase.

Step 3: Circumferential Mucosa Incision

Except for the pylorus or cardia, from the standard point of the angulus, the endoscopist makes the first incision at a point distal from the angulus (fig. 5). The endoscopist makes a small hole with a conventional needle knife or tip-noncovered type. The hole should reach below the muscularis mucosa. The appropriate depth will shorten the time needed for mucosal incision. Then the operator puts the IT knife into the hole. The IT knife should be used in a drawing manner from the distal point to the proximal point visually (fig. 4). Usually the line of the mucosal incision should be made outside of the marking line. The operator should always keep in mind the relationship between the direction of the IT knife's advancing line and the marking point. When the operator feels the elevation of mucosa injected with solution flatten, s/he should make additional injections of solution into the submucosa as necessary. In general, with the IT knife it is difficult to cut the mucosa in the transverse direction. If the operator feels difficulty in cutting the mucosa, s/he should change from the IT knife to a needle knife or tip-noncovered type device and the problem may be solved.

Step 4: Dissection of the Submucosal Layer

After the circumferential mucosal incision, the operator should start the submucosal dissection. Following the injection of solution into the submucosa, s/he starts dissecting from the right to the left or in the reverse direction in the submucosa (fig. 4). If the space is narrow, s/he makes space between the mucosa and the proper muscle layer by pushing the distal attachment into the narrow gap. The blade of the IT knife should be moved parallel to the proper muscle layer to avoid perforation. Too high a concentration of indigo carmine in the injection solution might mask the layer of the proper muscle, so it is better to keep the content of indigo carmine in the solution to a minimum. The operator sometimes encounters bleeding in submucosal dissection. If this occurs, s/he should remain calm and stop the bleeding with an endoscopic hemostat, for example, Coagrasper (FD-410LR, Olympus) using the water jet system. If the bleeding point is unclear, s/he might unconsciously continue some dissection near the bleeding point. Even while using the IT knife, s/he should avoid blind maneuvers so as to avoid perforation. When the operator is not able to inspect the lesion closely, s/he should change the position of the scope to retroflexed view, or deflate the air in the stomach to obtain a better view. In case the distance between the tip of endoscope and the dissecting point is large and bleeding or perforation occurs, it is difficult to perform the appropriate endoscopic treatment. If the operator finds large vessels during the dissection, s/he should do precoagulation of the vessels before cutting [13].

When the operator recognizes that the operation time may become too long or the general condition of patient is becoming worse, s/he should finish ESD as soon as possible. If the lesion has been resected except for only central connective tissue in the submucosa, s/he should use a big, stiff snare, such as the Captivator II (Boston Scientific Corp., Natick, Mass., USA) (fig. 6). If the lesion still remains large at this time point, s/he should choose either ending the procedure or removing the lesion using the two-channel EMR technique.

Following Resection of the Tumor

The operator should take care of bleeding or exposed vessels on the artificial ulcer base. Careful observation and diligent treatment of bleeding points or suspected bleeding with a hemostatic device after the resection could prevent late bleeding after ESD.

Generally speaking, the ESD specimen easily corresponds to the endoscopic finding before treatment because of less mucosal damage during the procedure, compared to EMR. The assessment of curative resection of ESD is as follows: EA is equivalent to curative resection; EB is not EA or EC; and EC is vertical margin (+) or lateral margin (+) (table 2) [14]. A patient with EC lesion should be recommended to undergo additional surgical resection with lymph node dissection. Treatment of the patient with EB lesion is controversial. In general, the patient with the lesion of vertical margin (+) or ly (+) or v (+) may be recommended to undergo surgical resection.

New Endosurgical Knives, New Endoscope, and Skillful Technique to Reduce Operation Time

New surgical knives have been developed. The IT knife-2 [15] is typical of the second generation of endosurgical knives (fig. 7a). It has a blade under the tip that enables transverse mucosal incision and submucosal dissection. Some papers have reported that the increased cutting ability of the IT knife-2 has increased the perforation rate but reduced the operation time. The dual knife is a second-generation needle type developed by Yahagi et al. [7] that has a small notch in the tip of the needle (fig. 7b). The FlushKnife BT was developed by Toyonaga et al. [9] (fig. 7c). These new knives have increased the ability to grasp or hook connective tissue in the submucosal layer. When the operator performs submucosal dissection, s/he uses one of the new knives, not tracing the surface of the submucosal layer, but slightly hooking it and turning on the current power.

When it is difficult to detect the lateral margin of the tumor, the use of magnifying observation with narrow band imaging is recommended. Yao et al. [16] reported that minute mucosal differentiated adenocarcinoma of the stomach has irregular microvessels, a demarcation line, and disappearance of regular crypt patterns. Figure 8 shows a lesion that is clearly indicated for ESD after the narrow band imaging illumination.

There are several difficult places that cannot be reached or observed easily during ESD using the GIF Q260-J, for example the incisura angularis or the anterior wall of the gastric body in the long and vertical type of stomach. The GIF Q260-2TM is a new endoscope for difficult ESD cases, and its second bending channel at the proximal part of the endoscope makes it easy to approach difficult locations for ESD using a regular scope. If you do not have new knives available and are not able to approach closely, you should change the GIF Q260-J to the GIF-2T (fig. 9). The latter scope has a much larger angle rate of retroflexion so that the operator is able to observe the lesion more closely.

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Fig. 5. Except for the pylorus and cardia, from the standard point of the angulus, the endoscopist makes the first incision at a point distal from the angulus.

Fig. 6. If the operator recognizes that the operation time may become too long or the general condition of patient is becoming worse, s/he should finish ESD as soon as possible. Operator should use a big, stiff snare, such as the Captivator II (Boston Scientific Corp., Natick, Mass., USA).

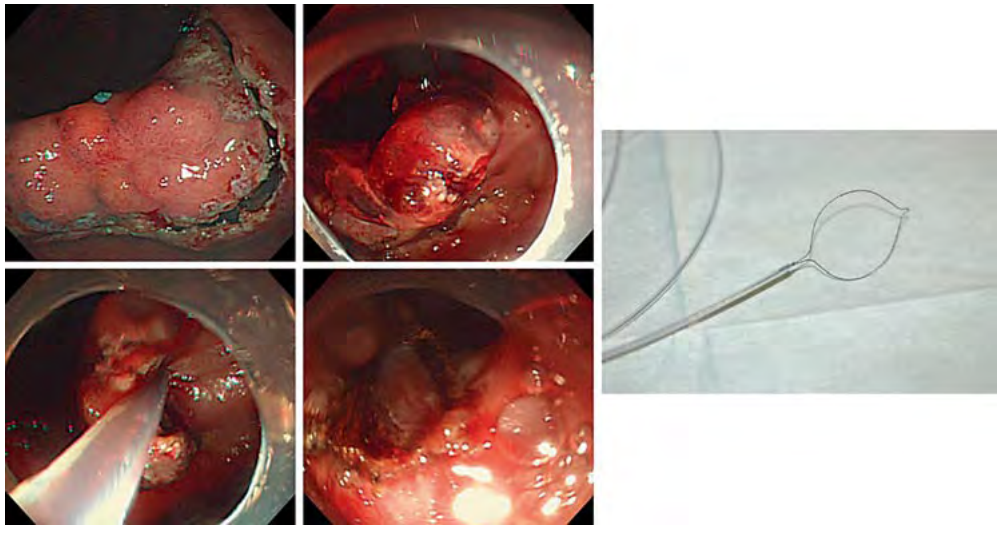

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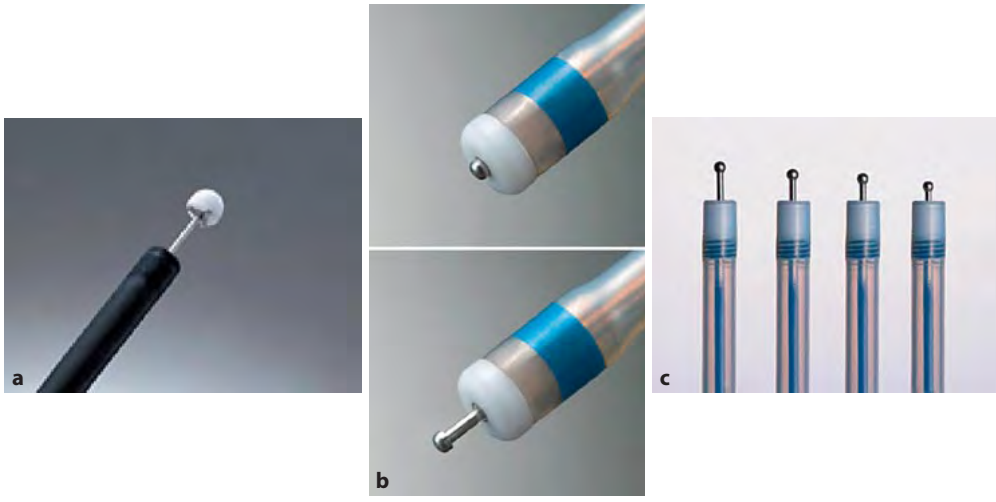
Table 2. Assessment of the resected specimen by endoscopic resection

	Depth	Histology	Ulceration	VM(–) LM(–)	LY • V
EA	M	PAP or TUB	(–)	VM(–) LM(–)	LY0 V0
EB	not EA or not EC				
EC	VM(+) or LM(–)				

PAP = Papillary adenocarcinoma, TUB = tubular adenocarcinoma, LY = Lymphatic invasion, V = microvessel invasion, VM = vertical margin, LM = lateral margin.



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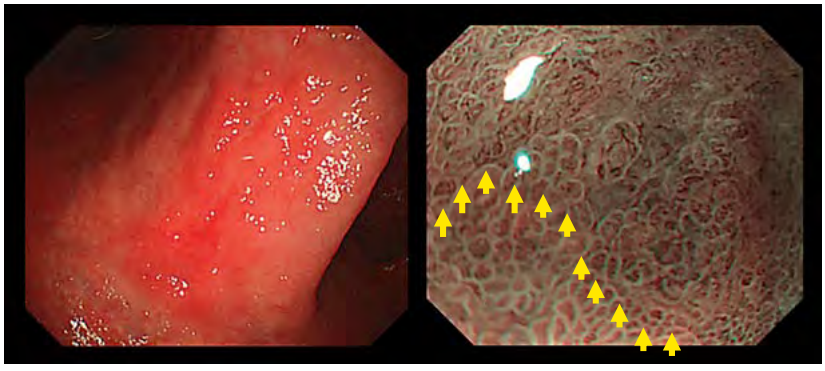

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Fig. 7. Second generation of ESD knives: the IT knife 2 (**a**), the dual knife (**b**), and the FlushKnife BT (**c**).

Fig. 8. The NBI illumination is able to indicate the margin of tumor clearly.

A shallow mucosal incision sometimes prolongs the ESD time. This figure shows the slightly yellow thin fibrosis band under the surface that is the muscularis mucosa. It disturbs the shrink of the lesion to the central point and is sometimes rich in vascular networks, which leads to bleeding (fig. 10). If the operator recognizes that the incision is shallow, s/he should perform additional trimming at the cut edge or a deeper incision under the muscularis mucosa.

Complications and Limitations

The operator should master how to solve the two major problems during ESD: bleeding and perforation. ESD cannot be performed without some degree of bleeding. We prepare the above-mentioned specific endoscope with a water jet system and the hemostatic devices against bleeding. The latter are the Coagrasper and hot biopsy. The tip of the Coagrasper is so sharp and rotational that the operator is able to grasp the vessel point to point. Coagulation should be selected as soft coagulation (80 W) (fig. 11).

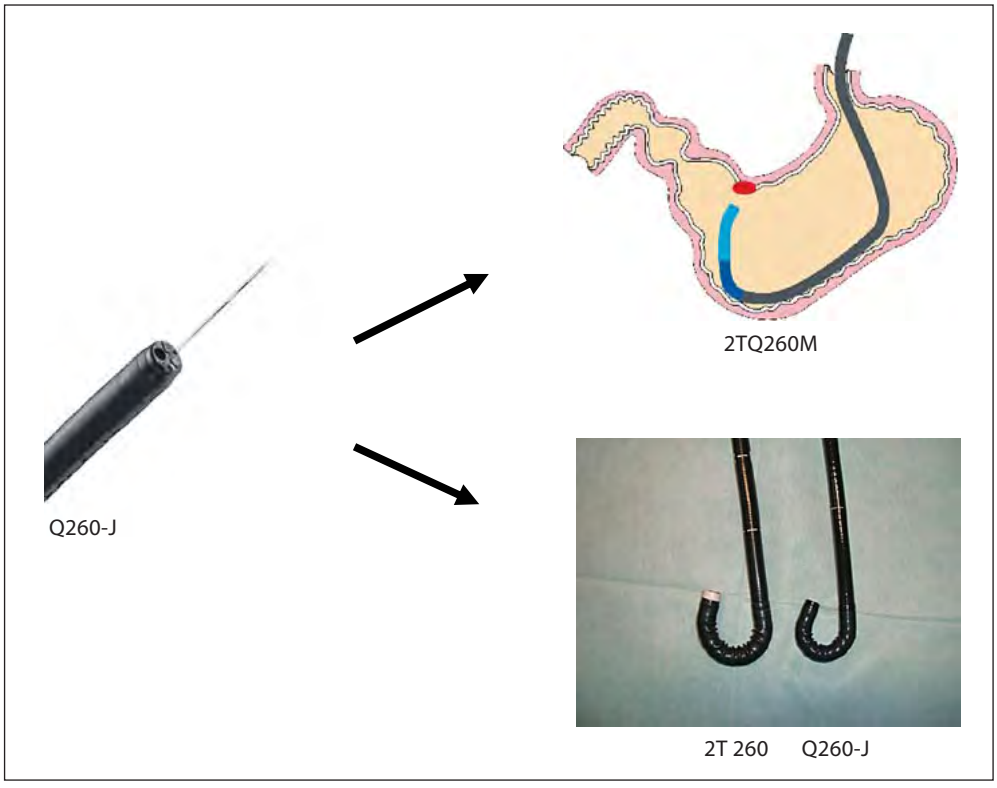
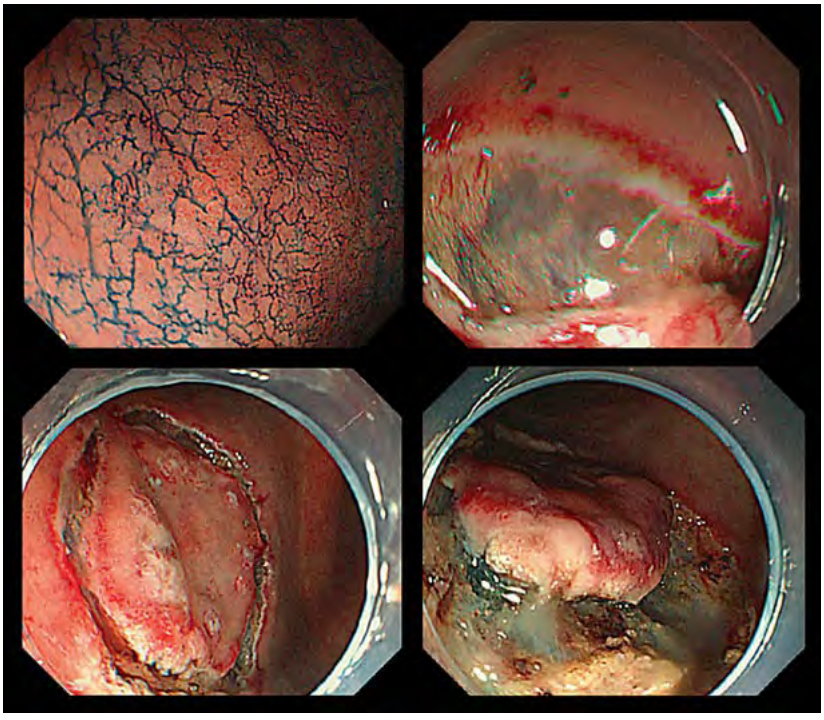


Fig. 9. If you are not able to approach the lesion closely, you should change the GIF Q260-J to the GIF-2T 260 or GIF 2TQ260M.

Perforation is a major complication but not a lethal one if the operator does the appropriate treatment immediately. It sometimes occurs while submucosal dissection is being performed blindly. The risk of perforation depends on the location, with the upper third of the body most prone to perforation, and presence of ulcer adding to the risk [17]. In addition, lesions on the greater curvature of the body are very difficult to inspect obliquely and to resect with IT knife (fig. 5). If the operator recognizes perforation during ESD, s/he should close it from the outside of the perforation using endoclips (HX-600-090; Olympus) or EX-clips (Olympus) (fig. 12). If the operator recognizes late that perforation has occurred and air has leaked from the stomach to the abdomen, s/he should deflate the air in the abdomen. If the general condition of the patient becomes worse, the operator or assistant should deflate air by inserting a catheter from the abdominal surface. From long-term observation, perforation has been reported not to induce the dissemination of gastric cancer [18].

Late bleeding and late perforation sometimes surprise the operator after ESD. Late perforation is believed to originate from too much coagulation at the ulcer bottom during ESD. The rate is unclear, but it occurs suddenly within 1–3 days after ESD. The hole of the perforation is sometimes very large and requires emergent surgical operation.



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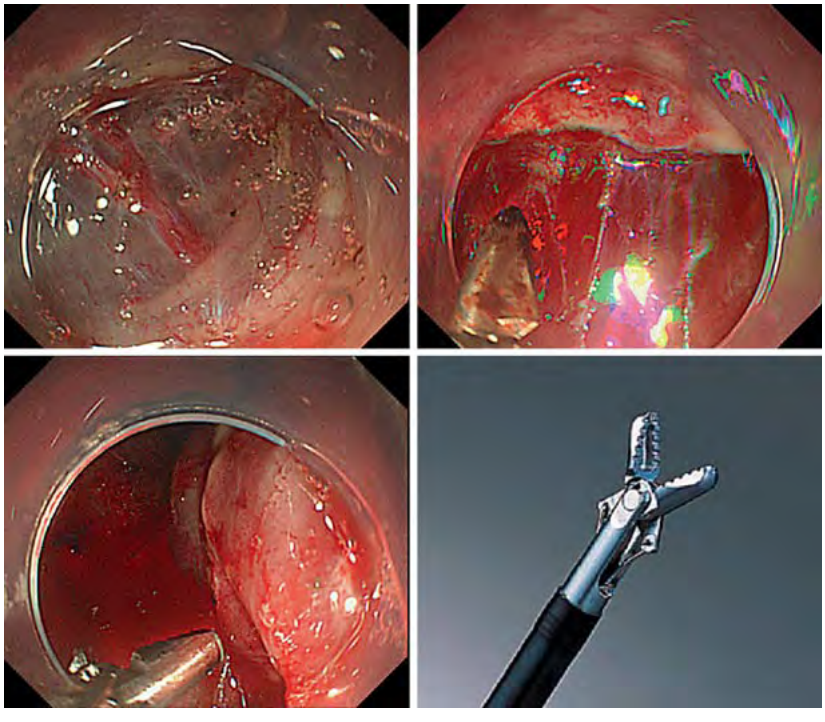

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Fig. 10. A shallow mucosal incision sometimes prolongs the ESD time. The slightly yellow thin band of fibrosis in the muscularis mucosa disturbs the shrink of the lesion to the central point.

Fig. 11. If a slightly large vessel in the submucosa is found, one should use precoagulation for it with soft coagulation (80 W) using Coagrasper (Olympus).

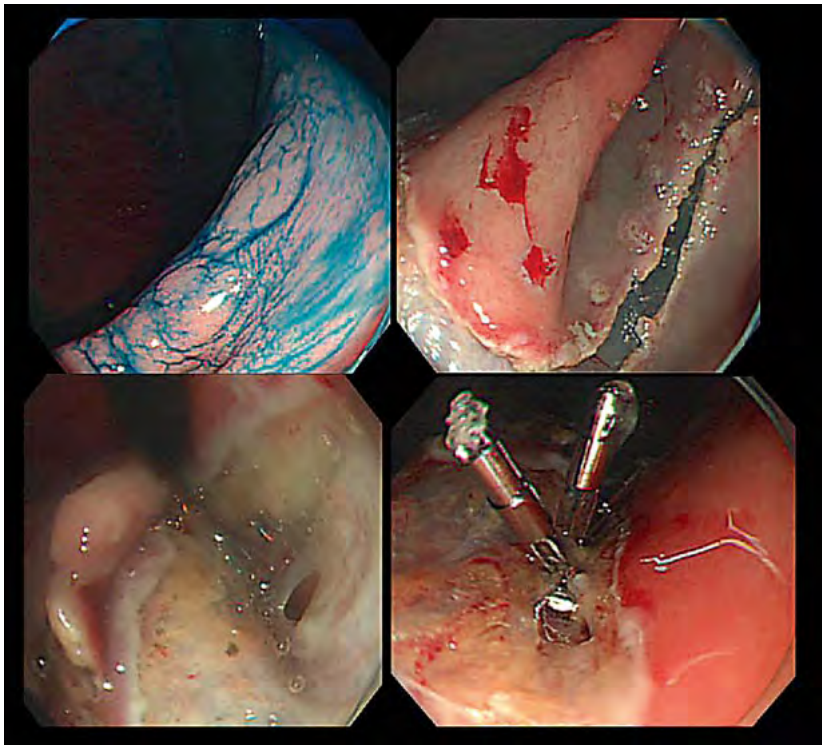

Fig. 12. If the operator recognizes perforation during ESD, s/he should close it from the outside of the perforation using endoclips (HX-600-090; Olympus) or EX-clips (Olympus).

Outcomes

The gastric cancer rate of recurrence in the EMR era was about 15%. This high rate resulted from piecemeal resection of the tumor during EMR. The recurrence rate of gastric cancer treated by ESD is significantly lower than that treated by EMR [4]. Uedo et al. [18] reported that the long-term disease-specific survival rate of EMR for small differentiated mucosal gastric cancer of <20 mm in diameter was 99%.

Conclusion

ESD has replaced EMR for superficial gastric neoplasm treatment in Japan. The drawbacks of ESD, such as a higher rate of complications, requirement for advanced endoscopic technique, and long procedure time, are being overcome with accumulated knowledge, consistently improving technique, and development of new devices and equipment. Even if we are able to remove larger neoplasms in the ESD era than in the EMR era, we need to be mindful of the indications for use of ESD and the histological results of resected specimens. It is necessary for the operator to keep in mind that the result of ESD *must be* equivalent to the result of surgical resection because, although the lesion is being removed without open surgery, it is early gastric cancer.

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