Endoscopic submucosal dissection for gastric neoplasia : Experience with the flex-knife

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Abstract

Although the standard treatment for gastric neoplasia is still surgical resection, endoscopic resection has been accepted for some of these lesions in an early stage. Among several methods of endoscopic resection, endoscopic submucosal dissection has been developed to remove the lesions in an en bloc fashion regardless of size, shape, coexisting ulcer, and location. However, indication of endoscopic submucosal dissection is strictly confined by two aspects ; those are the possibility of nodal metastases and technical difficulty. Nowadays, several knives for endoscopic submucosal dissection are available and each of them has some merits and demerits. We describe how to perform endoscopic submucosal dissection in the stomach by using the flex-knife, a new endoscopic device specifically designed for submucosal dissection, emphasizing its special features from our experience. (Acta gastroenterol. belg., **2006**, 69, **224-229**).

Key words : endoscopic submucosal dissection, flex-knife, gastric neoplasia, early cancer.

Introduction

Endoscopic resection could be theoretically indicated to the localized tumours without lymph node metastases. However, up to recently, the indication was limited to small lesions, because the conventional endoscopic resection method, that is endoscopic mucosal resection (EMR), is limited by the size of the lesion (1-13), as shown in extensive reviews of endoscopic resection (14-23). Endoscopic submucosal dissection (ESD) technique is a new endoscopic method using cutting devices, which remove the lesion by the following three steps : injection of fluid into the submucosa to elevate the lesion from the muscle layer, pre-cut of the surrounding mucosa of the lesion, and dissection of the connective tissue of the submucosa beneath the lesion. The major advantages of this technique in comparison with conventional EMR are : first, the resected size and shape can be controlled, second, en bloc resection is possible even in a large lesion, and third, the lesions with ulcerative findings are also resectable (24-38). Nowadays, several knives for ESD such as a needle knife (KD-1L-1, Olympus, Tokyo, Japan) (5, 29, 30), an insulated-tipped (IT) knife (KD-610L, Olympus) (24-28), a hook-knife (KD-620LR, Olympus) (35,36), a triangle-tipped (TT) knife (KD-640L, Olympus) (37,38), and a flex-knife (KD-630L, Olympus) (33,34) are available for ESD. Each of them has some merits and demerits, and the ways to use these various knives are different. We described here from our experience how to perform ESD for gastric neoplasia with special reference to the flex-knife.

Indications for ESD

Endoscopic resection is a local parietal treatment without lymph node dissection. So patients at no or small risk of lymph node metastases are the candidates for endoscopic treatment. Large surgical series have well described the risk of lymph node metastasis associated with different levels of mucosal and submucosal tumoural infiltration (39,40). Low risk tumours theoretically considered as good indications for endoscopic resection are as follows in the stomach :

➢ Intramucosal carcinoma :

1) Differentiated adenocarcinoma, irrespective of ulcer findings, < 3 cm in diameter,
2) Differentiated adenocarcinoma, without ulcer findings, > 3 cm in diameter
3) Undifferentiated adenocarcinoma, without ulcer findings, < 2 cm in diameter

➢ Submucosal carcinoma with minute submucosal penetration : Differentiated adenocarcinoma, < 500 μm below the muscularis mucosae, < 3 cm in diameter

However, preoperative prediction of the fulfilment of the above criteria is not possible in all the lesions, so that ESD can also be considered to obtain a histological evaluable en-bloc specimen (41) .

The indication of ESD should be discussed in a multidisciplinary team and may depend on local expertise, according to the technical achievements, determined by each institution or each operator. In our institution, all the lesions predicted preoperatively as fulfilling the above criteria, except for undifferentiated adenocarcinoma, are candidates for ESD. The reason why we are unwilling to treat undifferentiated adenocarcinoma is that endoscopic determination of the tumour margins is

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often difficult. Incomplete resection may therefore result in local recurrence or systemic tumoural spread.

Endoscopic systems & equipments

It is preferable to use a special slim endoscope that can spray water from the tip of the endoscope by footswitch to maintain a good vision during bleeding, if bleeding occurs (e.g. ; GIF-Q260J, Olympus, EG-2931, Pentax, Tokyo, Japan). Since several cutting and coagulation current may be used during ESD, we use a high-frequency electrosurgical unit with a special kind of cutting current, that is ENDOCUT mode, and two types of coagulation currents, those are forced mode and soft mode (Erbotom ICC 200, ERBE Elektromedizin GmbH, Tübingen, Germany). Devices and solutions necessary for ESD are listed below.

- Spraying tube for indigo carmine
- 0.25% indigo carmine
- 23-gauge injection needle for submucosal injection
- Submucosal injection solution : a 10% glycerine solution (Glyceol, Chugai pharmaceutical co., Tokyo Japan) with 0.0005% epinephrine and 0.005% indigo carmine is prepared for small distal gastric tumours without ulcer findings and a mixture of Glyceol and 1% 1900 KDa hyaluronic acid preparation (Suvenyl, Chugai pharmaceutical co. Tokyo Japan) are prepared for complex or proximal gastric tumours. Mixing ratio of Glyceol and Suvenyl is 7 :1 for complex or proximal gastric tumours (42-44)
- Flex-knife, (in case of difficulty encountered during resection by the flex-knife alone, other knives may be also prepared)
- Haemostatic forceps (FD-410LR, Olympus, or, SDB2422, Pentax)
- Transparent attachment which fits to the tip of an endoscope
- Spraying tube for sucralfate (45)
- Rotatable endoscopic clipping device for haemostasis or perforation closure
- Electrosurgical snare if snaring of the resected specimen is needed as the final step of resection.

Features of a flex-knife

There are several different features in the flex-knife (Fig. 1a) in comparison with the other knives (33, 34) .

➢ It has a soft, thick, and looped tip of the knife. So, being put onto the mucosa, the knife bends with appropriate tension and keeps constant position during mucosal cutting. During submucosal dissection, structure of the tip also acts well to prevent perforation.

➢ Length of the tip of the knife can be adjusted according to how to cut. Usually, its length is set about 1 mm for making marking dots (Fig. 1b), and about 2 mm for mucosal incision and submucosal dissection (Fig. 1c). If the knife is moved in parallel to the wall plane, the length may be adjusted longer than usual (about 3 mm) to make faster cutting. On the other hand, if the knife is applied in vertical to the wall plane, the length is adjusted shorter than usual (about 1 mm) to prevent deep cutting.

➢ The tip of the outer sheath is rolled over about 1 mm, which works as a stopper to keep constant incised depth.

➢ The outer sheath of the knife is thinner than the other knives, which results in good manoeuvrability to any direction with the wider range of appropriate working distance between the tip of the knife and the tip of the endoscope.

ESD procedure

The representative case of ESD is shown in Figure 2.

Marking around the lesion

After washing the stomach wall with sterile water containing small amount of dimethylpolysiloxane to remove mucus and gastric fluids, 0.25% indigo carmine is sprayed to clarify the border of the lesion. Circumferential markings are made by using a flex-knife at about 5 mm outside of the lesion with 2-mm intervals between each marking with the soft coagulation mode (output 50 W). Length of the tip of the knife is set to about 1 mm, and then its tip is pressed softly onto the mucosa, and the current is turned on only within a second.

Submucosal injection

The solution mentioned above is injected into the submucosal layer just outside the markings where mucosal incision intends to be made at first. The volume of injection is about 2 ml in one time, and injection is repeated several times before starting mucosal incision until the targeted area is lifting enough. Complete marginal cutting of the mucosa before submucosal dissection is not necessary, which means that mucosal incision and submucosal dissection are repeated several times before complete marginal cutting. After exposure of the submucosal layer, submucosal injection is applicable from the exposed submucosal layer to lift up the submucosal layer intended to cut.

Mucosal incision

After lifting the lesion, mucosal incision is started by using the same flex-knife. The tip of the knife is set to about 2 mm, pressed softly onto the mucosa, and the mucosa of outside the markings is incised circumferentially in ENDOCUT mode, effect 3 (output 80 W). The tip of the outer sheath of the knife is rolled over about 1 mm as a stopper, so the risk of perforation becomes extremely low if the knife is handled as the stopper does

Fig. 1. — Flex-knife and the length of it during endoscopic submucosal dissection
a. Flex-knife.
b. Length of the tip is set to about 1 mm for markings.
c. Length of the tip is set to about 2 mm for mucosal incision and submucosal dissection.

not hide inside the submucosa. The starting point for cutting depends on the location of the lesion. Principally, we start cutting from a distal part from the endoscope. Retroflex position of the endoscope is usually used if applicable when cutting the distal part of the lesion.

Submucosal dissection

Small lesions can be resected by an electrosurgical snare only after mucosal incision around the markings without submucosal dissection. However, large lesions, lesions with ulcer findings, or lesions located in a tortuous area cannot be resected by an electrosurgical snare, which needs dissecting the submucosa completely. Flex-knife is also used for dissecting the submucosa. The tip of the knife is set to about only 1 or 2 mm and submucosal dissection is made in forced coagulation mode (output 40 W). The knife is put slightly onto the connective tissue in the submucosal layer and the current is switched on intermittently for short bursts so that continuous adequate control and vision of the dissection can be maintained. If the target to dissect cannot be seen directly by any way, a transparent attachment on the tip of the endoscope is very useful to stretch the connective tissue and improve the field of viewing in the submucosa. The injected solution in the submucosa pours out after mucosal incision gradually and submucosal cushion flattens down as time has passed. So it is also important to start dissecting the submucosa immediately from the incising part of the mucosa before further marginal mucosal cutting and to re-inject into the submucosa if necessary to keep a security cushion.

Bleeding

Because haemostasis during bleeding is time-consuming, it is important to treat blood vessels with coagulation before bleeding may occur. For small vessels, which are smaller than the tip of the knife, the tip of a flex-knife is usually enough to treat them without changing to other devices and is used in the forced coagulation mode (output 40 W). For large vessels, haemostatic forceps should be used in soft coagulation mode (output 50 W).

However, all vessels cannot be managed before bleeding. Once bleeding occurs, immediate haemostasis is necessary. Coagulation using the tip of the knife or the haemostatic forceps is the first choice to achieve haemostasis with the same settings described above for non-bleeding vessels. In order to identify the bleeding points, splashing water from the tip of the endoscope is very useful. If the bleeding cannot be managed using the haemostatic forceps after coagulation for several times, haemostatic endoscopic clips can be used but may interfere with subsequent submucosal dissection.

Perforation

Perforation experienced during ESD by using a flex-knife is usually very small and noticed as soon as it occurs. When perforation occurs, immediate closure by endoscopic clipping is necessary in order not to deteriorate the patients' conditions. Tensional pneumoperitonium may be controlled by combining endoscopic clipping with percutaneous transabdominal air deflation using 18-gauge needle. In most cases with adequate perforation closure and medical treatment (no oral intake, resting, intravenous antibiotics), surgery may be avoided, if patients' condition and parameters improve (46). When the perforation is closed and the patient' condition is unremarkable, ESD procedure is usually pursued until completion of the resection.

Management of post ESD ulcer

After total removal of the lesion, all visible vessels located in the post-ESD ulcer base are treated using haemostatic forceps in soft coagulation mode (output 50 W). Finally, 20 ml of sucralfate liquid are sprayed using the outer sheath of the rotatable endoscopic clip device to confirm the achievement of correct haemostasis and coat the post-procedure ulcer base (45).

Management after ESD

After ESD, patients are prohibited eating and drinking until the next day of ESD. If laboratory findings and chest and abdominal X-ray remain unremarkable, then patients are permitted oral intake from soft foods. Follow-up endoscopy is performed within one week to check up post ESD ulcer healing before the patient is discharged from the ward. Proton pump inhibitor and

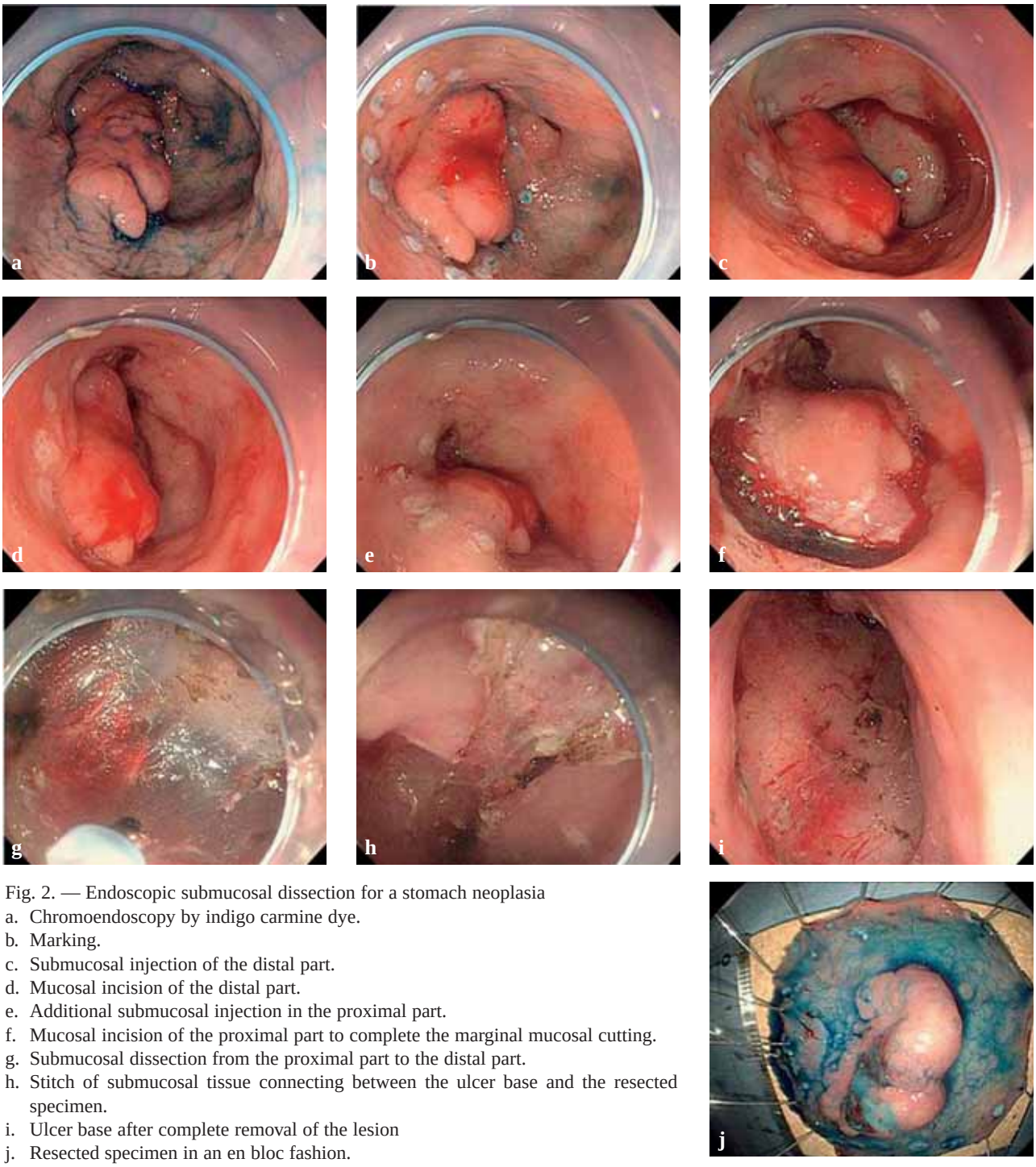

Fig. 2. — Endoscopic submucosal dissection for a stomach neoplasia
a. Chromoendoscopy by indigo carmine dye.
b. Marking.
c. Submucosal injection of the distal part.
d. Mucosal incision of the distal part.
e. Additional submucosal injection in the proximal part.
f. Mucosal incision of the proximal part to complete the marginal mucosal cutting.
g. Submucosal dissection from the proximal part to the distal part.
h. Stitch of submucosal tissue connecting between the ulcer base and the resected specimen.
i. Ulcer base after complete removal of the lesion
j. Resected specimen in an en bloc fashion.

sucralfate are administered until confirmation of healing of the post ESD ulcers. One recent study demonstrated that the administration of proton-pump inhibitors might be minimally effective for ulcer healing of endoscopic resection or only effective for bleeding complications after the procedure (47). Furthermore, a recent study revealed similar impact for ulcer healing by using famotidine in comparison with omeprazole (48). All patients with ESD also undergo a follow-up endoscopy 2 months after ESD to confirm the healing and exclude recurrence (48-50). In case of curative ESD en-bloc resection, annual endoscopies are performed to detect new metachronous lesions rather than recurrent tumour, since local recurrence rate is very low (41). For lesions with non-curative or non-evaluable resection margins, but fulfilling the criteria of node-negative tumours, upper GI endoscopy is performed every 6 months to detect local recurrent tumour, at least for three first years of follow-up.

Discussion

In the stomach, ESD has become a new "gold standard" modality of endoscopic treatment (22). It can be considered as an evolution of a previous EMR technique : endoscopic mucosal resection after local injection of a solution of hypertonic saline-epinephrine (ERHSE) (5). The technical difference between EMR and ESD is that the latter consists of an additional process of dissecting the submucosal layer under the tumour using electrosurgical knives. The merits of ESD over EMR are that the shape and the size of resected specimens can be controlled by operators and large tumours or ulcerative tumours can be resected in a single specimen. This is indeed important to decrease the rate of local recurrence generally observed after piece-meal resection (41). Furthermore, multi-fragmental resection may preclude adequate histopathological specimen analysis such as vessel infiltration, depth of invasion below the muscularis mucosae, or even the exact tumour size that are predictive factors of lymph node metastases. En bloc resection with ESD should therefore be considered as the "gold standard" method for gastric neoplasia when endoscopic curative resection is intended.

Several knives for ESD including the flex-knife are now available not only in Japan but also all over the world. Needle knife is the oldest and simplest knife among them, which enable to cut the tissue at the tip of the knife sharply. However, when applied in the vertical direction from the wall plane, the knife can easily pass through the stomach wall, which results in perforation. So it is advisable to employ a transparent endoscopic hood at the same time, and to use hyaluronic acid solution as an injection solution (29-31). To prevent the demerits of a needle knife, an IT-knife was invented first, which had a ceramic ball at the top of a needle knife (24-28). This knife is designed to protect the tip so that cutting cannot be achieved at the tip but at the needle blade. The way to use it is to put the ceramic ball in the submucosal layer to hook the mucosa or the submucosal connective tissue which is intended to be cut, and then pulling the knife. This is the only way to cut smoothly by using an IT-knife, so the knife sometimes has to be applied blindly, which may lead to complications such as bleeding and perforation (24-28, 52). The hook-knife which has a bending part at a right angle on the top of a needle knife was also invented for prevention of perforation but with different considerations (35,36). The direction of the hook can be controlled via handle rotation, which should be kept parallel with the wall plane to prevent perforation. However, to keep a constant and appropriate direction of the hook is sometimes difficult and a skillful assistant to handle the knife is necessary. This is the reason why the TT-knife, which has a triangular shaped metal plate attached to the tip of a needle knife, was invented to overcome the problems encountered with the hook knife (37,38). Indeed when the shape of the hook is triangular, there is no need to rotate the tip to hook the tissue intended to cut. It sounds reasonable, but thermal damage of the tissue by the tip of a rather large triangle plate may occur, damage the underlying muscle layer and preclude precise histological evaluation of the resected specimen.

No study has compared the relative efficiency and safety of the various knives used for ESD. Each of these has some advantages and disadvantages. The best knife would be the safest and the friendliest one to use. Each operator should be trained to use the appropriate one for the expected location and the specific technical difficulty and be able to switch to a more appropriate device. No one is perfect, although the flex-knife combines many qualities, such as direct dissection under full control of view and one single device used for marking, marginal cutting, submucosal dissection and haemostasis. ESD will become a more widely accepted method thanks to improvement of medical devices and better understanding and knowledge of the background, indications, procedures, and outcomes of ESD.

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