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REVIEW

CURRENT TECHNIQUES AND DEVICES FOR SAFE AND CONVENIENT ENDOSCOPIC SUBMUCOSAL DISSECTION (ESD) AND KOREAN EXPERIENCE OF ESD

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Conventional endoscopic mucosal resection (EMR) technique has limitations in its capacity of achieving en bloc resection and, for lesions greater than 20 mm, removal in a piecemeal resection is often required. This leads to uncertainty as to whether or not the lesion has been completely removed and to an increase in local recurrence. To overcome this limitation, a new technique using specifically designed cutting devices, termed endoscopic submucosal dissection (ESD) has been developed. The present article discuss the current indication, new diagnostic, cutting and hemostatic devices and long-term outcomes of EMR and ESD in early gastric cancer in Korea.

Key words: endoscopic submucosal dissection (ESD), device, outcome.

WHAT IS ESD?

Endoscopic submucosal dissection (ESD) is a new endoscopic treatment using cutting devices, which has developed from one of the endoscopic mucosal resection (EMR) techniques, namely endoscopic resection, after local injection of a solution of hypertonic saline-epinephrine (ERHSE). ESD consists of the following three steps: injecting fluid into the submucosa to elevate the tumor, pre-cutting the surrounding mucosa of the tumor, and dissecting the connective tissue of the submucosa beneath the tumor (Fig. 1). Major advantages of this technique in comparison with conventional EMR are as follows. The resected size and shape can be controlled, en bloc resection is possible even in a large tumor, and tumors with ulcerative findings are also resectable. Thus, this technique can be applied to the resection of complex tumors such as large tumors, ulcerative non-lifting tumors, and recurrent tumors. In one multicenter retrospective study in Korea, significant components influencing the recurrence after complete resection of early gastric cancer was the method of EMR.[1] According to this study, ESD and circumferential precutting followed by snare resection (EMR-P) were better than other conventional techniques, such as the injection and cutting method, EMR with transparent cap (EMR-C) and EMR with ligation (EMR-L), regarding the recurrence rate after complete resection. The disadvantages of this technique are the requirement for two or more assistants, it is time-consuming, with much more bleeding and a slightly higher perforation rate than with conventional EMR.

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INDICATION FOR ESD

Stomach

Although institutional differences in indications for endoscopic resection have existed for a long time, empirical indication for conventional EMR is differentiated-type mucosal cancers without ulcerative findings, and ≤2 cm in size if elevated or ≤1 cm in size if depressed or flat.[2]

Based on the reports by Gotoda *et al.* at the National Cancer Center and other groups, the indications for ESD in Japan at the present time are considered as: (i) non-ulcerated, differentiated-type mucosal carcinomas, regardless of tumor size; and (ii) differentiated-type mucosal carcinomas with an ulcer scar ≤30 mm (Table 1).[3]

Lesions meeting the above criteria should be resected endoscopically in one piece. According to the report from the National Cancer Center, no lymph node metastases have been noted among 1230 intramucosal cancers that met the conditions, including differentiated adenocarcinoma <3 cm in size without lymphatic or venous invasion, regardless of the presence or absence of an ulcer scar. In addition, 929 intramucosal cancers that met the conditions, including differentiated adenocarcinoma without ulcer scars and without lymphatic or venous invasion, did not show lymph node metastasis regardless of the size of the tumors.

These findings are the basis of the indication criteria described above (Table 2).[4]

Gotoda and colleagues have also shown that none of 145 patients with minute submucosal invasion and a differentiated early gastric cancer measuring <3 cm, without lymphatic-vascular involvement and with <500 μm of submucosal penetration (sm1) had nodal metastasis.[3]

Resected tissues are sectioned at 2 mm intervals and submitted for pathological evaluation. The treatment can be regarded as curative when a differentiated-type mucosal carcinoma without submucosal invasion or lymphatic or venous invasion is completely resected with its margin free of tumor.

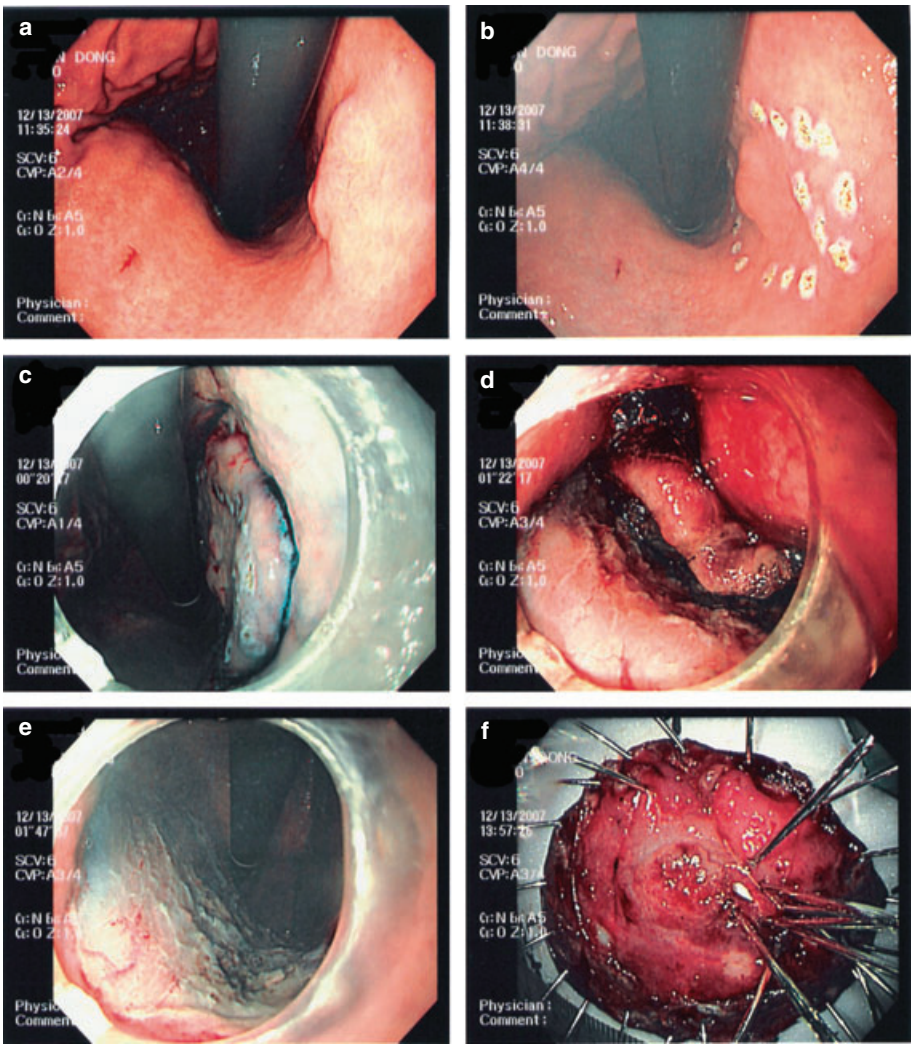

Fig. 1. Endoscopic submucosal dissection using the flex knife and IT knife. (a) Approximately 2 cm-sized flat elevated mucosal lesion was noted on the posterior wall of the mid body. (b) Marking with argon plasma coagulation was performed. (c) Circumferential incision was performed with flex knife. (d) Submucosal dissection with IT knife was performed. (e) Procedure was completed without complication. (f) Resected sample was a 22×16 mm-sized well-differentiated adenocarcinoma in a 50×40-mm sized specimen with clear resection margin.

Table 1. Incidence of lymph node metastasis in early gastric cancer

Criteria	Incidence	95% CI
Intramucosal cancer Differentiated adenocarcinoma No lymphovascular invasion Irrespective of ulcer findings Tumor <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
Intramucosal cancer Undifferentiated adenocarcinoma No lymphovascular invasion Without ulcer findings Tumor <3 cm in size	0/256; 0%	0–1.3
Minute submucosal invasion (sm1) Differentiated adenocarcinoma No lymphovascular invasion Tumor <3 cm in size	0/145; 0%	0–2.5

Esophagus

In esophageal squamous cell carcinoma, the risk of lymph node metastasis for m1 and m2 cancers is less than 2%, whereas cancers invading m3 and sm1 are associated with an 8% to 19% incidence of lymph node metastasis. In sm2 and sm3 cancers, the rate of lymph node metastasis increases to more than 40%.[5] In a study limited to patients with m3 and sm1 cancers, vertical diameter of depth of submucosal invasion within 200 μm was associated with a small risk of lymph node metastasis,[6] a subsequent study failed to confirm this results.[7]

The risk of lymph node metastasis in esophageal adenocarcinoma arising in Barrett's esophagus confined to the mucosal layer has been reported to be between 1% and 3%.[8,9] Also, two studies in which surgical and EMR specimens have been evaluated showed the results of no direct or indirect evidence of lymph node metastasis in m3 disease. When cancer invaded to the submucosal layer, there were no differences with regard to the risk of lymph node metastasis between adenocarcinoma and squamous carcinoma.[10]

Absolute indication for esophageal squamous cell carcinoma include superficial (m1, m2 lesions), limited (<3 cm, and <3/4 circumferential involvement), and few (one to four) lesions.[11] Relative indications include deep (m3 to sm1),

Table 2. Expansion of the criteria for local treatment

Histology	Depth					
	Mucosal cancer				Submucosal cancer	
	Ulcer (–)		Ulcer (+)		≤ sm1	> sm1
	≤2 cm	>2 cm	≤3 cm	>3 cm	≤3 cm	Any size
Differentiated	A	B	B	D	B	D
Undifferentiated	C	D	D	D	D	D

A, definite indication; B, expanded indication; C, surgery, but need for more consideration; D, surgery

extensive (>3 cm and >3/4 circumferential involvement), and multiple (>five) lesions.

Colon and rectum

The risk of lymph node metastasis in colon cancer occurs only after submucosal invasion and is directly correlated to the depth of submucosal invasion. The cut-off value at which the presence of submucosal invasion can be considered safe in endoscopically resected regimens has been estimated to be 500 μm by some authors,[12,13] but 1000 μm by others.[14] Colonic lymphatic and venules involvement has been found to be a better predictor of lymph node metastasis than depth of submucosal invasion.[15]

The indications for ESD in the treatment of colonic lesions are not yet established. ESD is applicable to lesions that have a higher rate of submucosal infiltration and that require detailed histological diagnosis by en bloc resection. These lesions include colorectal tumors with a diameter >20 mm and showing pit pattern types III_L, III_S, IV or low-grade V_I, and non-granular-type laterally spreading tumor, particularly those of the pseudodepressed type >20 mm in diameter. Large depressed tumors >10 mm, submucosal tumors arising intraluminally from the submucosal layer, and large tumors with fibrosis due to biopsy or other causes are considered to be relative indications for ESD.[16,17] Colorectal tumors with high-grade V_I or V_N pit patterns, or those with a positive non-lifting sign correspond to massive, submucosally invasive cancers, and ESD is not indicated in these cases because of the high risk of lymph node metastasis.

DIAGNOSTIC DEVICES

From 5% to 15% of early stage gastric cancers are multicentric, and accurate identification of the margins of gastric cancer is of considerable clinical importance, in particular for diffuse-type cancer, wherein the boundaries of the lesion are often indistinct and nests of tumor cells may be found at a distance from the grossly visible tumor margin.[18] Several new optical methods that could target malignant foci that are grossly unremarkable by white-light endoscopy have been evaluated.

Autofluorescence endoscopy and fluorescence diagnosis using a photosensitizer

Violet-blue light emitted by a laser source or short-arc xenon or mercury lamp provided with a special switching bandpass filter induces the emission of autofluoresence emitted by 'fluorophores', especially by submucosal collagen.[19] Several *in vitro* and *in vivo* studies show that the fluorescence emitted by tumorous gastric tissue or dysplastic Barrett's esophagus has a lower overall intensity than that emitted by normal mucosa.[20,21] Light-induced fluorescence endoscopy system can amplify the autofluorescence emitted by the lesion and helps to identify the margins of the cancer by color change. Overall reported sensitivity and specificity for the detection of malignant lesions in the stomach is approximately 84–94% and 85–87%, respectively, but decreases with decreasing degree of tumor differentiation, especially signet-ring cell.[22]

Photodynamic diagnosis using a fluorescence drug called a photosensitizer that reacts to various wavelengths of light is another spectroscopic technique. Fluorescence drugs, such as hematoporphyrin derivative (HPD) and Photofrin II (QLT Phototherapeutics, Vancouver, Canada), emit red fluorescence that can be detected by a special imaging device. Important factors associated with tumor tissue affinity to porphyrins have been examined via their strong affinity to for lipoprotein and active endocytosis in cancer cells associated with enhancement of low-density lipoprotein (LDL), and their transferring receptor activity. New photosensitizers, such as mono-L-aspartyl chlorin e6 (NPe6) (Meiji Seika, Tokyo, Japan), and ATX-S10 (Tokyo Hakka Co., Okayama, Japan) have been studied in an animal model and appear to be superior to HPD or Photofrin II for tumor affinity, and for reduced skin photosensitivity.[23]

Magnifying endoscopy

Observation of the microvascular architecture by magnifying endoscopy has been reported in the diagnosis of gastric cancer, and three characteristic findings in differentiated carcinoma: (i) the disappearance of the regular subepithelial capillary network pattern; (ii) the presence of an irregular microvascular pattern; and (iii) the presence of a demarcation line.[24,25] Enhanced magnification using acetic acid is an accurate method of predicting intestinal metaplasia in Barrett's esophagus and also in gastric dysplastic lesions.[26,27] In gastric mucosa, the duration of acetic acid-induced mucosal whitening differed among grades of neoplasia and after the disappearance of whitening in the carcinoma, the contrast between carcinomatous microvascular architecture and the whitened non-neoplastic tissue became very clear on magnifying endoscopy.[27]

Narrow band imaging

The narrow band imaging system is a video endoscopic imaging technique for enhanced display of mucosal

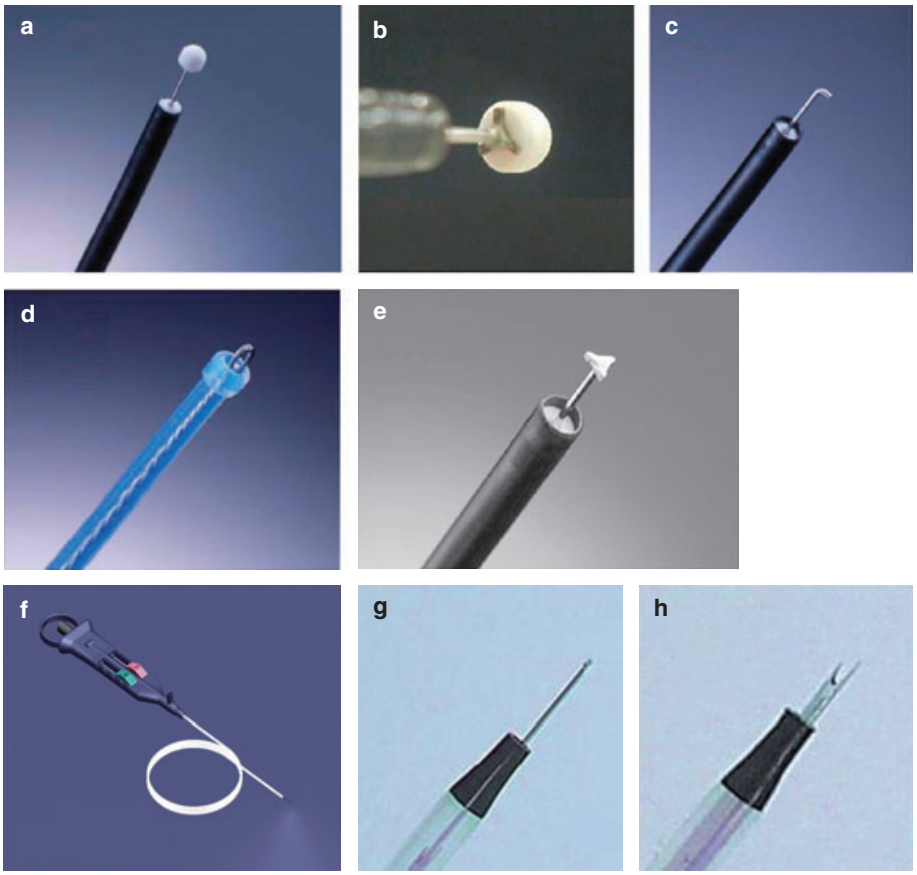

Fig. 2. Endo-knives used for endoscopic submucosal dissection. (a) IT knife, (b) modified IT knife, (c) Hook knife, (d) Flex knife, (e) triangular knife. Fork knives are shown in (f–h).

microstructure and capillaries of the superficial mucosal layer obtained when using narrow-band filters (wavelength range of the new RGB filters: 485–515 nm for red [R] 430–460 nm for green [G], and 400–430 nm for blue [B]), which are different from conventional filters, to the RGB of a plane sequential endoscope, and by changing the spectral feature of the observation light relative to that of the narrow band filters.

In the squamous epithelium, the intra-epithelial papillary capillary loop (IPCL) is observed by magnifying endoscopy with narrow band imaging. IPCL demonstrates characteristic change according to the tissue atypism and cancer invasion depth. IPCL type classification is directly related to the tissue characterization of a minute lesion.[28,29]

To distinguish Barrett's esophagus that contains specialized intestinal metaplasia from columnar-lined esophagus is difficult when using routine endoscopy, but combining an narrow-band imaging system and a magnifying endoscope allows simple and clear visualization of the micropattern of the superficial mucosal layer.[30] A study on the correlation between magnified images of the gastric mucosa obtained with the narrow band imaging system and the histological findings, especially with regard to the vascular pattern, showed the capability of the narrow band system predicting the histological characteristics of gastric cancer lesions.[31]

NOVEL THERAPEUTIC ENDOSCOPE

There are some tumor locations where it is difficult to carry out EMR using the conventional scope, for example, the lesser curvature or posterior wall of the gastric body, the cardia, and the lesser curvature of the antrum. To facilitate EMR of tumors at these locations, a two-channel scope with two independently curving segments, that is, a multibending scope (the 'M-scope') was developed.[32] The M-scope consists of a distal flexible segment that can bend in any of the four major directions and a proximal flexible segment that can bend in two directions. Combined operation of the segments allows the operator to obtain a variety of visual fields, to randomly approach or recede from the lesions, and to obtain an en face view.

Multibending double-channel therapeutic endoscope (the 'R-scope') has been designed for lifting lesions and for improved dissection by the incorporation of two movable channels.[33] The R-scope has two movable instrument channels: one moves vertically and the other swings horizontally. The two instruments can be manipulated during the operation with a knob and a lever that surround the angulation control knobs of the R-scope.

CUTTING DEVICES

Insulated-tipped knife

Various cutting devices are shown in Figure 2. The insulated-tipped diathermic knife (IT knife) consists of a small ceramic ball attached to the tip of a high-frequency needle knife.[34] The ceramic ball functions as an insulator of the tip of the needle knife so that incision and dissection of the mucosa and submucosa can be performed safely. The insulator helps to

prevent perforation due to accidental cutting of the muscularis propria.

In the IT knife method, physiological saline is primarily used as a submucosal injection fluid. A hole is made using a standard needle knife, allowing the insertion of the ceramic ball of the IT knife. Subsequently, the IT knife is used for the remaining procedures, including subsequent circumference incision of the intact mucosa surrounding the lesion and mucosal removal by dissection of the underlying submucosa.

A specialized feature of the IT knife, different from other incision instruments, is that the portion between the insulator tip and the sheath is used for incision, sweeping off the tissue with the blade portion of the knife instead of the tip. This is both an advantage and a disadvantage of this technique: it makes a pull-cut easier, whereas the direction of incision is limited, and straight-forward incision is difficult while looking directly at the incision line or submucosa.

Hook knife

The top of the hook-type knife is right-angled, 1 mm in size.[35] Compared to the use of a needle knife, safety is improved because the submucosal tissue is hooked and pulled before incision. Safety is further improved if it is used in conjunction with a transparent hood because tissue can then be pulled inside the hood. This knife has a rotating function so that the operator can select the optimal direction of the hook.

Flex knife

The point of the flex knife is rounded with a twisted wire, like a snare.[36] The sheath is soft and flexible. Compared to a needle knife, the flex knife is less likely to cause perforation when it reaches the muscular layer, as its tip is round, and the entire knife is soft and flexible. The length of the knife is adjustable for different situations. As the tip of the sheath is thick and functions as a stopper, operators can control the depth of incision very easily. A transparent hood is also helpful for better visualization of the operating field.

Triangle Tip knife

The Triangle Tip (TT) knife has evolved from the process of ESD, which began with the IT knife. The triangular tip of the knife can be used for either cutting or coagulating, and has been designed to operate in any direction.[37]

Fork knife

The fork knife was developed for simultaneous mucosal incision and submucosal dissection without the necessity for the exchange of accessory devices.[38] The thin needle knife is applied to the mucosal incision, and the serrated needle knife that injects the solution is applied to the submucosal dissection. The method of submucosal dissection is similar to the flex knife. After dissection of the proximal lesion, the lesion should be dissected moving more distally. The difference from the flex knife is that the fork knife is able to dissect submucosal tissue more effectively with the serrated knife and to shorten the dissection time for a wide contact surface. Also, in cases where submucosal solution injection is needed under the dissection, it can be done at once without the exchange of an accessory device, and so the duration of the procedure is shortened and there is a better visual field to help control any bleeding.

Forceps

New forceps with an incision function have been developed and allow more convenient ESD.[39]

INJECTION SOLUTIONS FOR ELEVATION

There are two types of solution for submucosal injection: an isotonic solution (normal saline, hyaluronic acid) and a hypertonic solution (hypertonic saline, glucose, Glyceol®).[40–42] The advantage of hypertonic solution is a better mucosal elevation and hemostatic effect than normal saline. But, hypertonic solution is more likely to damage tissue in a resection sample, post-resection ulcer, or the surrounding mucosa compared with isotonic solution. However, no definite tissue damage has developed using Glyceol®. Glyceol® is a mixture solution of 10% glycerin, 5% fructose and 0.9% NaCl. The glycerin of these solutions is not related with tissue damage because it is able to pass through the cell membrane freely. Hyaluronic acid preparation is a viscoelastic material different from other submucosal injection solutions. The advantages of hyaluronic acid preparation are as follows: local injection creates a more prominent and longer lasting mucosa protruding compared with normal saline solution; it does not flow out of the submucosa, even after incision of the mucosa and, because the injected solution persists locally for a long period of time, the effect of the epinephrine in the solution is long-lasting.

ACCESSORY DEVICES

Water jet

The water-jet system supplies a continuous jet of water at high pressure, which easily and swiftly washes away any blood that is obstructing the visual field, allowing identification of the bleeding source.[43] The water jet is delivered to the visual field by stepping on the foot switch. Because the water-jet system supplies water through an exclusive port, the forceps channel can be used for the hemostatic instrument. By washing the bleeding field with the water jet, the bleeding source can be immediately identified and coagulated, although in a small number of cases of erupting venous bleeding it can be difficult to identify the bleeding source. There are several hemostatic procedures which are used to control arterial bleeding during and after endoscopic submucosal dissection, but this procedure is quite effective and can be used as the method of first choice for treating this complication.

Tip hood

Irrigation hood-knife is the novel, semitransparent hood covers one-third of the tip circumference, facilitating endoscopic hemostatic procedures while simultaneously slowing irrigation of the bleeding site.[44] The irrigation tube and snare are glued to the exterior surface over the hole, and the snare

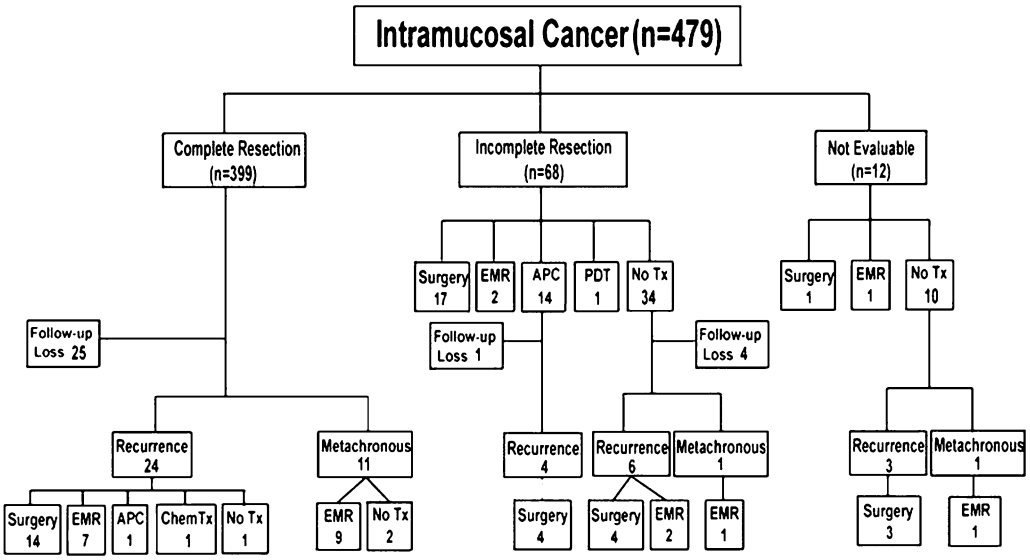

Fig. 3. Clinical course after endoscopic mucosal resection treatment for mucosal cancer.

is attached using short tubes on the inside of the cap. Submucosal exfoliation is carried out by sliding the hood-knife with coagulation current along the muscle layer. With this method, ESD can be safely and easily carried out under direct vision.

COMPLICATION-MANAGEMENT DEVICES

Bleeding is the most common complication, occurring in up to 7% of patients undergoing ESD.[45] 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, and endoclips are also often used for more brisk bleeding. High-frequency hemostatic forceps, forceps with rotation function, and endoscope equipped with a water-jet system are also developed and allow more effective bleeding control.[43]

Perforation is uncommon with EMR but is seen relatively more often with ESD. The risk of perforation during ESD is approximately 4%.[45] Perforations are typically closed with endoclips without peritoneal dissemination. Gastric perforation during endoscopic resection can be conservatively treated by complete endoscopic closure with endoclips.[46] 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.

KOREAN EXPERIENCE OF ESD FOR EARLY GASTRIC CANCER

I reviewed the experiences of ESD for early gastric cancer (EGC) in Korea (multicenter study by EMR study group of Korean gastrointestinal endoscopy society), with emphasis on the long-term outcome.[1]

The most commonly used technique was circumferential precutting followed by snare resection (EMR-P, $n = 269$, 52.3%). Complete resection and incomplete resection after

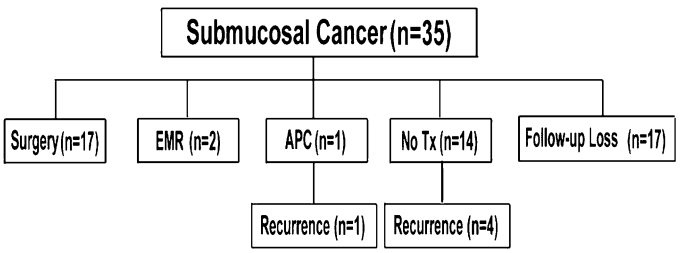

Fig. 4. Clinical course after endoscopic mucosal resection treatment for submucosal cancer.

EMR were confirmed in 399 lesions (77.6%) and 103 lesions (20.0%), respectively. For completely resected mucosal cancers ($n = 399$), the median duration of follow up was 23.5 months (range, 5–70). In this group, local recurrence was detected in 24 cases (6.0%) with a median interval between EMR and recurrence of 17.9 months (range, 3.5–51.7). The size of the lesion was the major factor determining the complete resection. The rate of complete resection for lesions with a diameter of ≤3 cm was 80.2% (368/459), whereas the rate for lesions >3 cm was 56.4% (31/55) (Figs 3,4). There were three cases with perforation and 71 cases with bleeding. There was no death related with recurrence of gastric cancer observed during the follow-up period, which had a median length of 39 months (Tables 3–5).

In the present study, the method of EMR was found to have a very highly significant association with the clinical outcome. Regarding the recurrence rate after complete resection of EGC, ESD and EMR-P were better than other conventional techniques. This result suggested that ESD and EMR-P had an advantage in the rate of en bloc resection and the length of cancer-free resection margin. Macroscopic type of lesion was also significant components influencing recurrence after complete resection, but this statistical significance was removed by a correction for multiple testing of data. Especially in cases with ulcer findings, the rate of recurrence was 50.0%, which was higher than for other types. Other factors including familial history of gastric cancer, tumor size,

Table 3. Macroscopic features classified according to tumor size

Type	≤1.0 cm	>1.0 cm and ≤2.0 cm	>2.0 cm and ≤3.0 cm	>3.0 cm	Total
Protruded	27	40	12	6	85 (16.5%)
Superficial elevated	27	64	21	28	140 (27.2%)
Superficial flat	18	37	11	9	75 (14.6%)
Superficial depressed	56	72	22	7	157 (30.5%)
Ulcerative	1	3	1	0	5 (1.0%)
Mixed	14	25	8	5	52 (10.1%)
Total	143 (27.8%)	241 (46.9%)	75 (14.6%)	55 (10.7%)	514 (100.0%)

Table 4. Rates of complete resection according to tumor size

	≤1.0 cm	>1.0 cm and ≤2.0 cm	>2.0 cm and ≤3.0 cm	>3.0 cm	Total
Complete resection	123 (86.0%)	183 (75.9%)	62 (82.7%)	31 (56.4%)	399 (77.6%)
Incomplete resection	17 (11.9%)	50 (20.7%)	12 (16.0%)	24 (43.6%)	103 (20.0%)
Not evaluable	3 (2.1%)	8 (3.3%)	1 (1.3%)	0 (0%)	12 (2.3%)
Total	143 (27.8%)	241 (46.9%)	75 (14.6%)	55 (10.7%)	514 (100.0%)

Table 5. Rates of complete resection according to tumor size

	Complete resection	Incomplete resection	Not evaluable	Total
Antrum	276 (81.4%)	56 (16.5%)	7 (2.1%)	339 (66.0%)
Angle	56 (71.8%)	20 (25.6%)	2 (2.6%)	78 (15.2%)
Low body	37 (68.5%)	15 (27.8%)	2 (3.7%)	54 (10.5%)
Mid body	11 (64.7%)	6 (35.3%)	0 (0%)	17 (3.3%)
Upper body	12 (75.0%)	3 (18.8%)	1 (6.3%)	16 (3.1%)
Fundus	1 (50.0%)	1 (50.0%)	0 (0%)	2 (0.4%)
Cardia	6 (75.0%)	2 (25.0%)	0 (0%)	8 (1.6%)

en bloc or piecemeal resection, *H pylori* infection and histological differentiation were found to have no influence on the recurrence after complete resection.

According to this multicenter study, the proportion of ESD among various EMR techniques was only 6.6%. Although the period of this study was between January 2000 and December 2002 and the proportion of ESD techniques is increasing in recent years in Korea, in my opinion, the extended criteria of EMR for EGC proposed by Soetikno *et al.*[4] was not as popular in Korea as in Japan.

REFERENCES

1. Kim JJ, Lee JH, Jung HY *et al*. EMR for early gastric cancer in Korea: A multicenter retrospective study. *Gastrointest. Endosc*. 2007; **66**: 693–700.
2. Tsujitani S, Oka S, Saito H *et al*. Less invasive surgery for early gastric cancer based on the low probability of lymph node metastasis. *Surgery* 1999; **125**: 148–54.
3. Gotoda T, Yanagisawa A, Sasako M *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**: 219–25.
4. Soetikno R, Kaltenbach T, Yeh R, Gotoda T. Endoscopic mucosal resection for early gastric cancer of the upper gastrointestinal tract. *J. Clin. Oncol*. 2005; **23**: 4490–8.
5. Kodama M, Kakegawa T. Treatment of superficial cancer of the esophagus: A summary of response to a questionnaire on superficial cancer of the esophagus in Japan. *Surgery* 1998; **123**: 432–9.
6. Watanabe H, Komokai S, Ajioka Y *et al*. Histopathology of m3 and sm1 invasive squamous cell carcinoma of the esophagus with special reference to endoscopic resection. *Stom. Intest*. 1998; **33**: 1001–9.
7. Eguchi T, Nakanishi Y, Shimoda T *et al*. Histopathological criteria for additional treatment after endoscopic mucosal resection for esophageal cancer: Analysis of 464 surgically resected cases. *Mod. Pathol*. 2006; **19**: 475–80.
8. Buskens CJ, Westerterp M, Lagarde SM *et al*. Prediction of appropriateness of local endoscopic treatment for

high-grade dysplasia and early adenocarcinoma by EUS and histopathologic features. *Gastrointest. Endosc*. 2004; **60**: 703–10.
9. Larchi A, Lightdale CJ, Memeo L *et al*. EUS followed by EMR for staging of high-grade dysplasia and early cancer in Barrett's esophagus. *Gastrointest. Endosc*. 2005; **62**: 16–23.
10. Bollschweiler E, Baldus SE, Schroder W *et al*. High rate of lymph-node metastasis in submucosal esophageal squamous-cell carcinoma and adenocarcinomas. *Endoscopy* 2006; **38**: 149–56.
11. Makuuchi H. Esophageal endoscopic mucosal resection (EEMR) tube. *Surg. Laparosc. Endosc*. 1996; **6**: 160–1.
12. Remacken BJ, Gotoda T, Fujii T *et al*. Endoscopic mucosal resection. *Endoscopy* 2001; **33**: 709–18.
13. Kodaira S, Yao T, Nakamura K. The incidence of lymph node metastasis of submucosal colorectal carcinomas in each submucosal invasion depth degree. Results from a questionnaire survey. *Stom. Intest*. 1994; **29**: 1137–42.
14. Yokoyama J, Ajioka Y, Watanabe H *et al*. Lymph node metastasis and micrometastasis of submucosal invasive colorectal carcinoma: An indicator of the curative potential of endoscopic treatment. *Acta Medica et Biologica* 2002; **50**: 1–8.
15. Aoki R, Tanaka S, Haruma K *et al*. MUC-1 expression as a predictor of the curative endoscopic treatment of submucosally invasive colorectal carcinoma. *Dis. Colon. Rectum* 1998; **41**: 1262–72.
16. Tanaka S, Oka S, Kaneko I *et al*. Endoscopic submucosal dissection for colorectal neoplasia: Possibility of standardization. *Gastrointest. Endosc*. 2007; **66**: 100–7.
17. Tamegai Y, Saito Y, Masaki N *et al*. Endoscopic submucosal dissection: A safe technique for colorectal tumors. *Endoscopy* 2007; **39**: 418–22.
18. Isozaki H, Okajima K, Hu X, Fujii K, Sako S. Mutiple early gastric carcinoma. Clinicopathologic features and histogenesis. *Cancer* 1996; **78**: 2078–86.
19. Izuishi K, Tajiri H, Fujii T *et al*. The histologic basis of detection of adenoma and cancer in the colon by autofluorescence endoscopic imaging. *Endoscopy* 1999; **11**: 108–18.
20. Abe S, Izuishi K, Tajiri H, Konoshita T, Matsuoka T. Correlation of in vitro autofluorescence endoscopy images with histopathologic findings in stomach cancer. *Endoscopy* 2000; **32**: 286–6.
21. Mayinger B, Jordan M, Horbach T *et al*. Evaluation of in vivo endoscopic autofluorescence spectroscopy in gastric cancer. *Gastrointest. Endosc*. 2004; **59**: 191–8.
22. Yano H, Iishi H, Tatsuta M. Diagnosis of gastric cancer by endoscopic autofluorescence imaging system. *Endoscopy* 1997; **29**: A–27.
23. Aizawa K, Nakamura K, Sheyhedin I. Optical biopsy with a fluorescence. *Clin. Gastroenterol*. 1999; **14**: 1177–84.
24. Yao K, Oishi T, Matsui T, Yao T, Iwashita A. Novel magnified endoscopic findings of microvascular architecture in intramucosal gastric cancer. *Gastrointest. Endosc*. 2002; **56**: 279–84.
25. Yao K, Oishi T. Microgastroscopic findings of mucosal microvascular architecture as visualized by magnifying endoscopy. *Dig. Endosc*. 2001; **13**: S27–33.
26. Goda K, Tajiri H, Ikegami M, Urashima M, Nakayoshi T, Kaise M. Usefulness of magnifying endoscopy with narrow band imaging for the detection of specialized intestinal metaplasia in columnar-lined esophagus and Barrett's adenocarcinoma. *Gastrointest. Endosc*. 2007; **65**: 36–46.
27. Yagi K, Aruga Y, Sekine A, Umezu H. The study of dynamic chemical magnifying endoscopy in gastric neoplasia. *Gastrointest. Endosc*. 2005; **62**: 963–9.
28. Inoue H, Honda T, Nagai K *et al*. Ultra-high magnification endoscopic observation of carcinoma in situ of the esophagus. *Dig. Endosc*. 1997; **9**: 16–18.
29. Inoue H. Magnifying endoscopy in the esophagus and stomach. *Dig. Endosc*. 2001; **13**: 40–1.
30. Sharma P, Bansal A, Mathur S *et al*. The utility of a novel narrow band imaging endoscopy system in patients with Barrett's esophagus. *Gastrointest. Endosc*. 2006; **64**: 155–66.
31. Nakayoshi T, Tajiri H, Matsuda K, Kaise M, Ikegami M, Sasaki H. Magnifying endoscopy combined with narrow band imaging system for early gastric cancer: Correlation of vascular pattern with histopathology. *Endoscopy* 2004; **36**: 1080–4.
32. Isshi K *et al*. The effectiveness of a new multibending scope for endoscopic mucosal resection. *Endoscopy* 2004; **36**: 294–7.
33. Yonezawa J *et al*. Modified therapeutic endoscope for ESD of superficial gastric neoplasm. *Endoscopy* 2006; **38**: 1011–15.
34. Ohkuwa M, Hosokawa K, Boku N *et al*. New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. *Endoscopy* 2001; **33**: 221–6.
35. Oyama T, Kikuchi Y. Aggressive endoscopic mucosal resection in the upper GI tract-hook knife EMR method. *Minim. Invasive Ther. Allied Technol*. 2002; **11**: 291–5.
36. Yahagi N, Fujishiro M, Kakushima N *et al*. Endoscopic submucosal dissection for early gastric cancer using the tip of an electro-surgical snare (thin type). *Dig. Endosc*. 2004; **16**: 34–8.
37. Inoue H, Sato Y, Kazawa T *et al*. Endoscopic submucosal dissection-using a triangle-tipped knife (in Japanese). *Stom. Intest*. 2004; **39**: 53–6.
38. Jung IS. Skill and pitfall of endoscopic incision and submucosal dissection. *Korean J. Gastrointest. Endosc*. 2005; **31** (Suppl. 1): 93–7.
39. Yamamoto H, Seike Y, Higashizawa T *et al*. Successful en bloc resection of a large superficial gastric cancer by using sodium hyaluronate and electrocautery incision forceps. *Gastrointest. Endosc*. 2001; **54**: 629–32.
40. Uraoka T, Fujii T, Saito Y *et al*. Effectiveness of glycerol as a submucosal injection for EMR. *Gastrointest. Endosc*. 2005; **61**: 736–40.
41. Fujishiro M *et al*. Successful outcomes of a novel endoscopic treatment for GI tumors: Endoscopic submucosal dissection with a mixture of high-molecular-weight hyaluronic acid, glycerin, and sugar. *Gastrointest. Endosc*. 2006; **63**: 243–9.
42. Akahoshi K, Yoshinaga S, Fujimaru T *et al*. Endoscopic resection with hypertonic saline-solution-epinephrine injection plus band ligation for large pedunculated or semipedunculated gastric polyp. *Gastrointest. Endosc*. 2006; **63**: 312–16.
43. Enomoto S *et al*. Endoscopic hemostasis technique for use during endoscopic submucosal dissection. *Endoscopy* 2007; **39**: E156.
44. Kume K, Yamasaki M, Kanda K, Yoshikawa I, Otsuki M. Endoscopic submucosal dissection using a novel irrigation hood-knife. *Endoscopy* 2005; **37**: 1030–1.
45. Oda I, Gotoda T, Hamanaka H *et al*. Endoscopic submucosal dissection for early gastric cancer: Technical feasibility, operation time and complications from a large consecutive series. *Dig. Endosc*. 2005; **17**: 54–8.
46. Ono H, Kondo H, Gotoda T *et al*. Treatment of esophageal and gastric tumors. *Endoscopy* 1999; **31**: 47–55.