Management of bleeding and artificial gastric ulcers associated with endoscopic submucosal dissection

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Abstract
Endoscopic submucosal dissection (ESD), an endoscopic procedure for the treatment of gastric epithelial neoplasia without lymph node metastases, spread rapidly, primarily in Japan, starting in the late 1990s. ESD enables en bloc resection of lesions that are difficult to resect using conventional endoscopic mucosal resection (EMR). However, in comparison to EMR, ESD requires a high level of endoscopic competence and a longer resection time. Thus, ESD is associated with a higher risk of adverse events, including intraoperative and postoperative bleeding and gastrointestinal perforation. In particular, because of a higher incidence of intraoperative bleeding with mucosal incision and submucosal dissection, which are distinctive endoscopic procedures in ESD, a strategy for endoscopic hemostasis, mainly by thermo-coagulation hemostasis using hemostatic forceps, is important. In addition, because of iatrogenic artificial ulcers that always form after ESD, endoscopic hemostasis and appropriate pharmacotherapy during the healing process are essential.

Key words: Artificial ulcer; Endoscopic hemostasis; Endoscopic submucosal dissection; Gastric epithelial neoplasia; Hemostatic forceps

INTRODUCTION
Endoscopic submucosal dissection (ESD) is a novel endoscopic procedure developed in the 1990s[1,2], and is characterized by the use of electrosurgical knives for mucosal incision and submucosal dissection.[3-15]. In ESD, the resected size and shape of tumors can be controlled, and even lesions difficult to resect by endoscopic mucosal resection (EMR) can be resected en bloc by ESD. As this technique permits en bloc resection of tumors, ESD has the advantages of enabling accurate pathological assessment and reducing the risk of local recurrence.[2,16-19]. However, ESD requires a higher level of endoscopic competence than EMR. In addition, as a result of ESD being used to treat larger lesions and lesions with ulcerative findings, operation time is longer, with a higher risk of adverse events, including intraoperative and postoperative bleeding and gastrointestinal perforation. In particular, because of a higher incidence of intraoperative bleeding with mucosal incision and submucosal dissection, which are distinctive endoscopic procedures in ESD, a strategy for endoscopic hemostasis, mainly by thermo-coagulation hemostasis using hemostatic forceps, is important. In addition, because of iatrogenic artificial ulcers that always form after ESD, endoscopic hemostasis and appropriate pharmacotherapy during the healing process are essential.
of adverse events such as bleeding and gastrointestinal perforation\textsuperscript{[20-29]} \textsuperscript{22.6\%}. The incidence of procedure-related bleeding is higher with ESD than with EMR, and to permit safe completion of ESD, control of bleeding is very important. In this article, we discuss the characteristics of ESD-related bleeding (intraoperative and postoperative bleeding) and endoscopic hemostasis. Furthermore, to prevent postoperative bleeding, we also discuss the pharmacotherapy of artificial ulcers after ESD.

**ENDOSCOPIC HEMOSTASIS USING HEMOSTATIC FORCEPS**

Endoscopic hemostatic methods for peptic ulcers include various techniques, such as local injection of hypertonic saline-epinephrine (HSE) and ethanol, mechanical hemostasis using endoscopic hemoclips, and thermo-coagulation hemostasis\textsuperscript{[30,31]}. Local injection of HSE alone is inferior to combination therapy with other hemostatic methods, but the clear superiority of any one method has not been definitively established\textsuperscript{[32]}. Thermo-coagulation devices include contact thermal devices such as heater probes and hemostatic forceps, and non-contact thermal devices such as an argon plasma coagulator\textsuperscript{[33,34]}.

For hemostasis of ESD intraoperative bleeding, Enomoto \textit{et al.}\textsuperscript{[35]} reported the usefulness of a method of thermo-coagulation hemostasis using monopolar hemostatic forceps in combination with an endoscope equipped with a water-jet system. Hemostatic technique in ESD, which differs from hemostasis for usual gastrointestinal bleeding, is often characterized by the need for repeated hemostasis during both mucosal incision and submucosal dissection. In addition, precise hemostatic maneuvers are required, in order not to interfere with the subsequent procedure after hemostatic treatment\textsuperscript{[36,37]}. Therefore, hemostatic forceps, which enable control of hemostasis when, with re-holding of the ruptured vessels permissible several times before coagulation, bleeding points can be accurately grasped, are useful for hemostasis in ESD-related bleeding\textsuperscript{[38,39]} (Figure 1).

With wider use of ESD, hemostasis using hemostatic forceps has become routine at medical centers, and its usefulness for bleeding from exposed vessels at the base of peptic ulcers has also been reported\textsuperscript{[40,41]}. Moreover, the usefulness not only of monopolar, but also of bipolar hemostatic forceps, has been reported\textsuperscript{[42]}.

**MANAGEMENT OF BLEEDING DURING AND AFTER ESD**

ESD-related bleeding includes intraoperative bleeding associated with procedures such as mucosal incision and submucosal dissection, and delayed bleeding, which occurs postoperatively from exposed vessels at ulcer bases. Appropriate management of each type of bleeding is required.

**Endoscopic hemostasis for intraoperative bleeding**

In ESD, the incidence of intraoperative bleeding, which is to some degree unavoidable given the nature of techniques such as incision and dissection, is as high as 22.6\%\textsuperscript{[22.6\%]}. In particular, with ESD for lesions in the upper third of the stomach, because of abundant vessels in the submucosa, the incidence of intraoperative bleeding is relatively high\textsuperscript{[43]}. To predict intraoperative bleeding, identification of the submucosal vascular structure by preoperative endoscopic ultrasonography can be useful\textsuperscript{[44]}. Of the series of techniques in ESD, bleeding is inevitable with submucosal local injection and mucosal incision because they are blind procedures in the vascular-rich submucosal tissue. To produce higher hemostatic ability, a small amount of epinephrine to a concentration of 0.0005\% is added to the submucosal cushion (glycele, Chugai Pharmaceutical Co., Tokyo Japan). On the other hand, during submucosal dissection, bleeding can be avoided at all sites by making every effort to visually identify vessels and not perform dissection blindly. Oyama \textit{et al.}\textsuperscript{[30,31]} noted that identification of vessels prior to submucosal dissection and prophylactic thermo-coagulation are most important in preventing ESD intraoperative bleeding. Toyonaga \textit{et al.}\textsuperscript{[13,46]} stated that knowing the correct layer of the submucosa containing fewer vessels and existing fibrous tissue, is important in reducing ESD intraoperative bleeding.

When bleeding occurs during ESD, by washing out the blood with the water-jet system and using a transparent attachment hood, a clear visual field can be maintained, and bleeding points can be rapidly identified\textsuperscript{[45]}. For bleeding from vessels smaller than the electrosurgical knife tip or arm, hemostasis by thermo-coagulation with the knife is usually possible. For bleeding from vessels larger than the electrosurgical knife tip or arm, or bleeding for which hemostasis with the knife is difficult, hemostatic forceps are used (Figure 2). Fujishiro \textit{et al.}\textsuperscript{[47]} reported that hemostatic forceps for vessels smaller than 2 mm in diameter, and hot biopsy forceps for vessels larger than 2 mm in diameter, are useful. When hemostasis by thermo-coagulation cannot be achieved, hemostasis using endoscopic hemoclips is necessary, so that subsequent procedures are not hindered.

**Hemostasis for delayed bleeding**

Delayed bleeding after ESD occurs in 0%-9\% of cases\textsuperscript{[6,16,18,28,48-54]} (Table 1). For resected lesions located in the middle and lower third of the stomach, the incidence is higher. Bleeding occurs when vessels at ulcer bases rupture due to physical stimulation by peristalsis or due to chemical stimulation, for example, by bile reflux\textsuperscript{[48]}. Delayed bleeding often occurs within 24 h postoperatively and is related to lesion location, size, and ulcer findings\textsuperscript{[48,55]}. For delayed bleeding, in almost all cases, hemostasis is achieved with urgent endoscopic hemostasis\textsuperscript{[56]}. However, cases requiring vascular embolization because endoscopic hemostasis could not be achieved\textsuperscript{[57]} and cases complicated by disseminated intravascular coagulation the day after delayed bleeding\textsuperscript{[58]} have been reported, so caution is necessary.
To prevent delayed bleeding, prophylactic coagulation of exposed vessels at the bases of artificial ulcers that occur after ESD lesion resection is very useful. According to Takizawa et al.\textsuperscript{[59]}, the cause of delayed bleeding is due more to insufficient prophylactic thermo-coagulation than insufficient primary hemostasis during ESD\textsuperscript{[60]}, because the site of delayed bleeding is not the site of endoscopic hemostasis during surgery. In addition, a study has been conducted on the prevention of delayed bleeding by evaluation of blood flow at ulcer bases using endoscopic Doppler ultrasound (US). Uedo et al.\textsuperscript{[61]}, based on blood flow detected using Doppler US, reported that, by coagulation of vessels seen at artificial ulcer bases after ESD lesion resection, delayed bleeding is reduced, and unnecessary thermo-coagulation of vessels without blood flow can be avoided. On the other hand, Choi et al.\textsuperscript{[62]} reported that prophylactic closure of gastric EMR-induced ulcers with metal hemoclips prevent delayed bleeding.

In 2008, a survey of treatment methods for peptic and artificial ulcer bleeding was conducted at nine departments of high-volume center hospitals in Japan\textsuperscript{[63]}. For endoscopic hemostasis of peptic ulcer bleeding, the number one method used was clipping (32.9%), followed by coagulation forceps (23.5%). In contrast, for artificial ulcer bleeding, coagulation forceps (77.8%) were used significantly more. In addition, the proportion of patients who underwent second-look endoscopy, compared to peptic ulcers, was significantly lower for artificial ulcers (86% and 71%, respectively).

The effectiveness of second-look endoscopy after hemostasis of peptic ulcer bleeding has previously been shown\textsuperscript{[64,65]}. However, according to Goto et al.\textsuperscript{[66]}, for artificial ulcers, no significant difference in the incidence of delayed bleeding before and after second-look endoscopy was found. This suggests that delayed bleeding after ESD, irrespective of whether second-look endoscopy is performed, may develop. However, for artificial ulcers located in the lower third of the stomach, because delayed bleeding occurs earlier, careful follow-up observation or early second-look endoscopy may be useful\textsuperscript{[54,66]}.

### Table 1  Delayed bleeding rate of endoscopic submucosal dissection for gastric epithelial neoplasia

| Author      | Year | Total cases | Delayed bleeding (%) | En bloc resection rate (%) |
|-------------|------|-------------|----------------------|---------------------------|
| Oda et al.  | 2005 | 945         | 6                    | 93                        |
| Kakushima et al.  | 2006 | 383         | 3.4                  | 91                        |
| Imagawa et al.  | 2006 | 196         | 0                    | 93                        |
| Onozato et al.  | 2006 | 171         | 7.6                  | 94                        |
| Oka et al.  | 2006 | 195         | 6.2                  | 83                        |
| Hirasaki et al.  | 2007 | 112         | 7.1                  | 96                        |
| Ono et al.  | 2008 | 161         | 8.7                  | 99                        |
| Hoteya et al.  | 2009 | 572         | 4.9                  | 95                        |
| Isomoto et al.  | 2009 | 510         | 1.8                  | 95                        |
| Tsuji et al.  | 2010 | 398         | 5.8                  | NA                        |
| Akasaka et al.  | 2011 | 1188        | 3.1                  | 95                        |

NA: Not analyzed.
MANAGEMENT OF ARTIFICIAL GASTRIC ULCERS AFTER ESD

Pharmacotherapy of artificial ulcers that develop after ESD lesion resection is also important to prevent delayed bleeding. However, management must take into account the differences in etiology between peptic ulcers and artificial ulcers after ESD.

Comparison of peptic ulcers and artificial ulcers
Currently, proton pump inhibitors (PPIs) are the drugs of first choice for treatment of peptic ulcers, and when a PPI cannot be used, an H2-receptor antagonist (H2RA) is selected. Treatment is generally for 8 wk. A meta-analysis of ulcer healing rates reported significantly higher ulcer healing rates with PPIs than with H2RAs[67,68]. In addition, in a meta-analysis of the efficacy of preventing recurrence of bleeding gastric ulcers, no differences in rebleeding rates, surgical intervention rates, or mortality rates between the two classes of drugs were reported[69].

The etiology of artificial ulcers after gastric ESD and peptic ulcers also differs greatly[70]. First, peptic ulcers develop, at least in part, due to hyperacidity, whereas artificial ulcers form in a hypoacidic environment in which there is severe mucosal atrophy. Second, peptic ulcers develop at sites where there is breakdown of gastric mucosal defense mechanisms, whereas artificial ulcers occur iatrogenically at sites where mucosal defense mechanisms are intact. Third, peptic ulcers include ulcers deeper than the submucosa, and inflammation spreads in the ulcer periphery, whereas artificial ulcers, because they basically occur due to submucosal dissection, are relatively shallow ulcers down to the submucosa, and the inflammation is localized. Despite these differences, treatment of an artificial ulcer after gastric ESD, based on treatment for a peptic ulcer, is empiric, with an anti-acid drug for 8 wk[63] (Table 2).

Anti-acid drugs for artificial ulcers
For artificial ulcers that develop after ESD for gastric mucosal lesions without preoperative ulcer findings, Kakushima et al[71] reported that healing occurred within 8 wk with PPI administration for 8 wk, irrespective of ulcer size or location. In addition, factors that influence artificial ulcer healing such as artificial ulcer size, location, Helicobacter pylori infection status, and extent of gastric mucosal atrophy had no effect. However, with fibrosis deeper than the submucosa of lesions prior to ESD, healing may be delayed[72,73]. According to Huang et al[74], although the recurrence rate of ESD artificial ulcers is lower than that of peptic ulcers, Helicobacter pylori infection and lesion ulcer findings are risk factors for recurrence. In contrast, Oh et al[75] reported that, because the extent of healing of artificial ulcers 4 wk after ESD is determined by the size of the ulcer initially formed, the duration of PPI treatment should be decided based on this parameter.

For artificial ulcers after EMR, Lee et al[76] compared PPIs in 1-wk and 4-wk treatment groups. They found that, after 4 wk, ulcer size, stage, subjective symptoms, and use of other mucosal-protective anti-ulcer drugs did not significantly differ between the groups. Niimi et al[77] reported that administration of PPI for 2-wk for artificial ulcers after ESD may be sufficient to help them heal. These results suggest that, for artificial ulcers, unlike peptic ulcers, the importance of acid secretion inhibition
in the ulcer healing process may be low.

Yamaguchi et al. compared PPI-treatment and H2RA-treatment groups in patients with artificial ulcers after EMR. They reported no differences in the incidence of delayed bleeding or ulcer size at 30 d and 60 d postoperatively: They did state that artificial ulcers healed more easily than peptic ulcers, and they concluded that, for artificial ulcers with severe bleeding within 24 h after surgery, treatment with H2RA drugs, whose onset of inhibition of gastric acid secretion is more rapid than that with PPIs, is appropriate.

Uedo et al. compared PPI-treatment and H2RA-treatment groups in patients with artificial ulcers after ESD. There were no differences in the incidence of delayed bleeding or ulcer healing rates between the groups. However, the cumulative non-bleeding rate using the Kaplan-Meier method was significantly higher in the PPI group. Moreover, on multivariate analysis, PPI treatment was an independent factor in reducing the rate of delayed bleeding. Their results suggested that PPIs are more effective than H2RAs for preventing ESD delayed bleeding.

For post-EMR ulcers and post-ESD ulcers, in terms of formation by endoscopic resection, with the exception of size, the pathophysiology is the same. However, in studies to date, with regard to ulcer healing and prevention of delayed bleeding when artificial ulcers are treated with acid secretion inhibitors, there is no agreement in the results. Regarding the need for and duration of treatment with acid secretion inhibitors for artificial ulcers, there is still room for debate.

### Mucosal-protective antiulcer drugs in artificial ulcers

In the treatment of peptic ulcers, there is no evidence that combined therapy with a PPI and a mucosal-protective antiulcer drug is superior to a PPI alone. However, in artificial ulcers, an additive effect of mucosal-protective antiulcer drugs has been reported (Table 2). Asakuma et al. compared combined therapy with a PPI (rabeprazole 20 mg/d) and ecabt sodium (3.0 g/d) vs the PPI alone for artificial ulcers after ESD. At 4 wk and 8 wk, ulcer healing rates were significantly higher in the combined treatment group. In addition, Kato et al. compared combined therapy with a PPI (rabeprazole 10 mg/d) and rebamipide (300 mg/d) vs the PPI alone for artificial ulcers after ESD. At 4 wk, the ulcer scarring rate was significantly higher in the combined treatment group. Similarly, Fujisawa et al. compared combined therapy with a PPI (rabeprazole 20 mg/d) and rebamipide (300 mg/d) vs the PPI alone for artificial ulcers after ESD. At 8 wk, the ulcer scarring rate was significantly higher in the combined treatment group.

Thus, among the mucosal-protective antiulcer drugs, there are drugs that accelerate ulcer healing. This may be attributable to differences in the etiology between artificial ulcers and peptic ulcers, as previously mentioned, but further evidence must be accumulated.

### CONCLUSION

With the increasing use of ESD for gastric epithelial neoplasia, management of ESD-related bleeding and artificial ulcers after lesion resection has become an important issue not only in Japan, but throughout the world. Therefore, more effective endoscopic hemostatic methods and appropriate pharmacotherapy of artificial ulcers, taking into account their etiology, are becoming increasingly important. Moreover, safer and more reliable ESD techniques must be developed.

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### REFERENCES

1. Fujishiro M. Endoscopic submucosal dissection for stomach neoplasms. World J Gastroenterol 2006; 12: 5108-5112
2. **Kakushima N**, Fujishiro M. Endoscopic submucosal dissection for gastrointestinal neoplasms. *World J Gastroenterol* 2008; 14: 2962-2967

3. **Ono H**, Kondo T, Gotoda T, Shino K, Yamaguchi H, Saito D, Hosokawa K, Shimoda T, Yoshida S. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001; 48: 225-229

4. **Ohkusa M**, Hosokawa K, Boku N, Ohtu A, Tairini H, Yoshida S. New endoscopic treatment for intramural gastric tumors using an insulated-tip diathermic knife. *Endoscopy* 2001; 33: 221-226

5. **Gotoda T**. A large endoscopic resection by endoscopic submucosal dissection procedure for early gastric cancer. *Clin Gastroenterol Hepatol* 2005; 3: S71-S73

6. **Ono H**, Hasuikue N, Inui T, Takizawa K, Ikehara H, Yamaguchi Y, Otake Y, Matsubayashi Y. Usefulness of a novel electroesurgical knife, the insulation-tipped diathermic knife-2, for endoscopic submucosal dissection of early gastric cancer. *Gastric Cancer* 2008; 11: 47-52

7. **Oyama T**, Kikuchi Y. Aggressive endoscopic mucosal resection in the upper GI tract-hook knife EMR method. *Minim Invasive Ther Allied Technol* 2002; 11: 291-295

8. **Yamamoto H**, Kawata H, Sunada K, Sasaki A, Nakazawa K, Miyata T, Sekine Y, Yano T, Satoh K, Ido K, Sugano K. Successful endo-bloc resection of large superficial tumors in the stomach and colon using sphygmology and small-caliber-tip transparent hood. *Endoscopy* 2005; 35: 690-694

9. **Inoue H**, Kudo S. A novel procedure of en block EMR using triangle-tipped knife (abstract). *Gastrointest Endosc* 2003; 57: A86

10. **Yahagi N**, Fujishiro M, Kakushima N, Kobayashi K, Hashimoto T, Oka M, Iuchi G, Enomoto S, Ichinose M, Niwa H, omata M. Endoscopic submucosal dissection for early gastric cancer using the tip of an electrosurgical snare (thin type). *Dig Endosc* 2004; 16: 34-38

11. **Fujishiro M**, Yahagi N, Nakamura M, Kakushima N, Kodashima S, Ono S, Kobayashi K, Hashimoto T, Yamachii N, Tateishi A, Shimizu Y, Oka M, Ogura K, Kawabe T, Ichinose M, Omata M. Endoscopic submucosal dissection for rectal epithelial neoplasia. *Endoscopy* 2006; 38: 493-497

12. **Fujishiro M**, Yahagi N, Kakushima N, Kodashima S, Muraki Y, Ono S, Yamamichi N, Tateishi A, Shimizu Y, Oka M, Ogura K, Kawabe T, Ichinose M, Omata M. Endoscopic submucosal dissection of esophageal squamous cell neoplasms. *Clin Gastroenterol Hepatol* 2006; 4: 685-694

13. **Toyonaga T**, Nishimine E, Dozai T, Ueda C, Hirooka T. Management to prevent bleeding during endoscopic submucosal dissection using the flush knife for gastric tumors. *Dig Endosc* 2007; 19 Suppl 1: S14-18

14. **Fujishiro M**, Kodashima S, Goto O, Ono S, Muraki Y, Kakushima N, Omata M. Successful endo-bloc resection of superficial esophageal cancer treated by endoscopic submucosal dissection with a splash needle. *Endoscopy* 2008; 40 Suppl 2: E81-E82

15. **Akahoshi K**, Akahane H. A new breakthrough: ESD using a newly developed grasping type scissors forceps for early gastrointestinal tract neoplasms. *World J Gastroenterol* 2010; 2: 90-96

16. **Oka S**, Tanaka S, Kaneko I, Mouru R, Hirata M, Kawamura T, Yoshihara M, Chayama K. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. *Gastrointest Endosc* 2006; 64: 877-883

17. **Watanabe K**, Ogata S, Kawazoe S, Watanabe K, Koyama T, Kajiwara T, Shimoda Y, Takase Y, Irie K, Mizuguchi M, Tsunada S, Iwakari R, Fujimoto K. Clinical outcomes of EMR for gastric tumors: historical pilot evaluation between endoscopic submucosal dissection and conventional mucosal resection. *Gastrointest Endosc* 2006; 63: 776-782

18. **Imagawa A**, Okada H, Kawahara Y, Takenaka R, Kato J, Kawamoto H, Fujiki S, Takata R, Yoshino T, Shiratori Y. Endoscopic submucosal dissection for early gastric cancer: results and degrees of technical difficulty as well as success. *Endoscopy* 2006; 38: 987-990

19. **Isomoto H**, Yamaguchi N. Endoscopic submucosal dissection in the era of proton pump inhibitors. *J Clin Biochem Nutr* 2009; 44: 205-211

20. **Fujishiro M**, Yahagi N, Kakushima N, Kodashima S, Muraki Y, Ono S, Kobayashi K, Hashimoto T, Yamamichi N, Tateishi A, Shimizu Y, Oka M, Ogura K, Kawabe T, Ichinose M, Omata M. Successful nonsurgical management of perforation complicating endoscopic submucosal dissection of gastrointestinal epithelial neoplasms. *Endoscopy* 2006; 38: 1001-1006

21. **Fujishiro M**. Perspective on the practical indications of endoscopic submucosal dissection of gastrointestinal neo-plasms. *World J Gastroenterol* 2008; 14: 4289-4295

22. **Fujishiro M**. Endoscopic submucosal dissection for gastric cancer. *Curr Treat Options Gastroenterol* 2008; 11: 119-124

23. **Tanaka M**, Ono H, Hasuikue N, Takizawa K. Endoscopic submucosal dissection of early gastric cancer. *Digestion* 2008; 77 Suppl 1: 23-28

24. **Cao Y**, Liao C, Tan A, Gao Y, Mo Z, Gao F. Meta-analysis of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. *Endoscopy* 2009; 41: 751-757

25. **Chung IK**, Lee JH, Lee SH, Kim SJ, Cho JY, Cho WY, Hwangbo Y, Keum BR, Park JJ, Chun HJ, Kim HJ, Kim JJ, Ji SR, Seol SY. Therapeutic outcomes in 1000 cases of endoscopic submucosal dissection for early gastric neoplasms: Korean ESD Study Group multicenter study. *Gastrointest Endosc* 2009; 69: 1228-1235

26. **Conlin A**, Kaltenbach T, Kusano C, Matsuda T, Oda I, Gotoda T. Endoscopic resection of gastrointestinal lesions: advancement in the application of endoscopic submucosal dissection. *J Gastroenterol* 2010; 25: 1348-1357

27. **Onogi F**, Araki H, Ibuka T, Manabe Y, Yamazaki K, Nishiwaki S, Moriwaki H. “Transmural air leak”: a computed tomographic finding following endoscopic submucosal dissection for gastric tumors. *Endoscopy* 2010; 42: 441-447

28. **Akasaka T**, Nishida T, Tsutsumi S, Michida T, Yamada T, Ogiyama H, Kitamura S, Ichiba M, Komori M, Nishiyama O, Nakanishi F, Zushi S, Nishihara A, Iijima H, Tsuji M, Hayashi N. Short-term outcomes of endoscopic submucosal dissection (ESD) for early gastric neoplasm: multicenter survey by osaka university ESD study group. *Dig Endosc* 2011; 23: 75-77

29. **Kim YJ**, Park DK. Management of complications following endoscopic submucosal dissection for gastric cancer. *World J Gastrointest Endosc* 2011; 3: 67-70

30. **Conway JD**, Adler DG, Diehl DL, Farraye FA, Kantsevoy SV, Kaul V, Kethu SR, Kwon RS, Mamula P, Rodriguez SA, Tierney WM. Endoscopic hemostatic devices. *Gastrointest Endosc* 2009; 69: 987-996

31. **Anjiki H**, Kamisawa T, Sanaka M, Iishi T, Kuyama Y. Endoscopic hemostasis techniques for upper gastrointestinal hemorrhage: A review. *World J Gastrointest Endosc* 2010; 2: 54-60

32. **Adler DG**, Leighton JA, Davila RE, Hirota WK, Jacobson BC, Qureshi WA, Rajan E, Zuckerman MJ, Fanelli RD, Hambrick RD, Baron T, Faigel DO. ASGE guideline: The role of endoscopy in acute non-variceal upper-GI hemorrhage. *Gastrointest Endosc* 2004; 60: 497-504

33. **Watson JP**, Bennett MK, Griffin SM, Matthesson K. The tissue effect of argon plasma coagulation on esophageal and gastric mucosa. *Gastrointest Endosc* 2000; 52: 342-345

34. **Fujishiro M**, Yahagi N, Nakamura M, Kakushima N, Kodashima S, Ono S, Kobayashi K, Hashimoto T, Yamamichi N, Tateishi A, Shimizu Y, Oka M, Ichinose M, Omata M. Safety of argon plasma coagulation for hemostasis during endoscopic mucosal resection. *Surg Laparosc Endosc Percutan Tech*
[35] Enomoto S, Yahagi N, Fujishiro M, Oka M, Kakushima N, Iguchi M, Yanoaka K, Ariti K, Tamai H, Shimizu Y, Omata M, Ichinose M. Novel endoscopic hemostasis technique for use during endoscopic submucosal dissection. Endoscopy 2007; 39 Suppl 1: E156

[36] Enomoto S, Yahagi N, Fujishiro M, Iguchi M, Ichinose M. Endoscopic hemostasis using high-frequency hemostatic forceps for hemorrhagic gastric ulcer. Nihon Rinsho 2004; 62: 513-518

[37] Enomoto S, Yahagi N, Fujishiro M, Oka M, Muraki Y, Deguchi H, Ueda K, Inoue I, Makita T, Magari H, Mukouyabashi C, Nakazawa K, Iguchi M, Yanoaka K, Ariti K, Tamai H, Omata M, Ichinose M. Assessment of intraoperative bleeding during endoscopic submucosal dissection and endoscopic hemostasis using high-frequency hemostatic forceps. J Wakuamai Med 2009; 60: 124-129

[38] Fujishiro M, Abe N, Endo M, Kawahara Y, Shimoda R, Nagata S, Homma K, Morita Y, Ueda N. Retrospective multicenter study concerning electrocautery forceps with soft coagulation for nonmalignant gastroduodenal ulcer bleeding in Japan. Dig Endosc 2010; 22 Suppl 1: S15-S18

[39] Yoshida N, Naito Y, Kugai M, Inoue K, Wakabayashi N, Yagi N, Yanagisawa A, Yoshikawa T. Efficient hemostatic method for endoscopic submucosal dissection of colorectal tumors. World J Gastroenterol 2010; 16: 4180-4186

[40] Nagata S, Kimura S, Ogoshi H, Hidaka T. Endoscopic hemostasis of gastric ulcer bleeding by hemostatic forceps coagulation. Dig Endosc 2010; 22 Suppl 1: S22-S25

[41] Cournarios D, Tsesmeli N. Active gastrointestinal bleeding: use of hemostatic forceps beyond endoscopic submucosal dissection. World J Gastroenterol 2010; 16: 2061-2064

[42] Kataoka M, Kawai T, Yagi K, Tachibana C, Tachibana H, Sugimoto H, Hayama Y, Yamamoto K, Nonaka M, Aoki T, Oshima T, Fujiwara M, Fukuzawa M, Fukuzawa M, Kawakami K, Sakai Y, Moriyasu F. Clinical evaluation of emergency endoscopic hemostasis with bipolar forceps in non-variceal upper gastrointestinal bleeding. Dig Endosc 2010; 22: 151-155

[43] Hiro M, Masuda K, Asanuma T, Naka H, Noda K, Matsurka K, Yamaguchi O, Ueda N. Endoscopic resection of early gastric cancer and other tumors with local injection of hypertonic saline-epinephrine. Gastrointest Endosc 1988; 34: 264-269

[44] Kikuchi D, Iizuka T, Hoteya S, Yamashita S, Nakamura M, Kuroki Y, Mitani T, Fujimoto A, Matsu A, Nishida N, Yahagi N. Usefulness of endoscopic ultrasound for the prediction of intraoperative bleeding of endoscopic submucosal dissection for gastric neoplasms. J Gastroenterol Hepatol 2011; 26: 68-72

[45] Oyama T, Tomori A, Hotta K, Miyata Y. Hemostasis with hook knife during endoscopic submucosal dissection. Dig Endosc 2006; 18 Suppl 1: S128-S130

[46] Toyonaga T, Nishino E, Hirooka T, Ueda C, Noda K. Intraoperative bleeding in endoscopic submucosal dissection in the stomach and strategy for prevention and treatment. Dig Endosc 2006; 18 Suppl 1: S123-S127

[47] Fujishiro M, Yahagi N, Kakushima N, Kodashima S, Muraki Y, Tateishi A, Omata M. Management of bleeding concerning endoscopic submucosal dissection with the flex knife for stomach neoplasm. Dig Endosc 2006; 18 Suppl 1: S119-S122

[48] Oda I, Gotoda T, Hamanaka H, Eguchi T, Saito Y, Matsuda T, Bhandari P, Emura F, Saito D, Ono H. Endoscopic submucosal dissection for early gastric cancer: technical feasibility, operation time and complications from a large consecutive series. Dig Endosc 2005; 17: 54-58

[49] Kakushima N, Fujishiro M, Kodashima S, Muraki Y, Tateishi A, Omata M. A learning curve for endoscopic submucosal dissection of gastric epithelial neoplasms. Endoscopy 2006; 38: 991-995

[50] Onozato Y, Ishihara H, Iizuka H, Sohara N, Kakizaki S, Okamura S, Mori M. Endoscopic submucosal dissection for early gastric cancers and large flat adenomas. Endoscopy 2006; 38: 980-986

[51] Hirasa K, Kanazaki H, Matsubara M, Fujita K, Ikeda F, Taniguchi H, Yumoto E, Suzuki S. Treatment of over 20 mm gastric cancer by endoscopic submucosal dissection using an insulation-tipped diathermic knife. World J Gastroenterol 2007; 13: 3981-3984

[52] Hoteya S, Iizuka T, Kikuchi D, Yahagi N. Benefits of endoscopic submucosal dissection according to size and location of gastric neoplasm, compared with conventional mucosal resection. J Gastroenterol Hepatol 2009; 24: 1102-1106

[53] Isomo H, Shikuwa S, Yamaguchi N, Fukuda E, Ikeda K, Nishiyama H, Ohnita K, Mizuta Y, Shiozawa J, Kohno S. Endoscopic submucosal dissection for early gastric cancer: a large-scale feasibility study. Gut 2009; 58: 331-336

[54] Tsuji Y, Oka H, Ito T, Chiba H, Ohya T, Gunji T, Matsuhashi N. Risk factors for bleeding after endoscopic submucosal dissection for gastric lesions. World J Gastroenterol 2010; 16: 2931-2937

[55] Gotoda T, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. J Gastroenterol 2006; 41: 929-942

[56] Messmann H, Probst A. Management of endoscopic submucosal dissection complications. Endoscopy 2009; 41: 712-714

[57] Lee CK, Park JY, Lee TH, Lee SH, Chung JK, Park SH, Kim HS, Kim SJ. Superselective microcoil embolization for endoscopically uncontrollable bleeding after endoscopic submucosal dissection. Endoscopy 2009; 41 Suppl 2: E109-E110

[58] Kang SH, Kim JI, Kim EM, Moon HS, Kim SH, Lee BS, Sung JK, Jeong HY. A rare case of disseminated intravascular coagulation after endoscopic submucosal dissection for early gastric cancer. Endoscopy 2010; 42 Suppl 2: E33-E34

[59] Takizawa K, Oda I, Gotoda T, Yokoi C, Matsuda T, Saito Y, Saito D, Ono H. Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection—an analysis of risk factors. Endoscopy 2008; 40: 179-183

[60] Okano A, Hafiro K, Takakuwa H, Nishio A, Matsushita M. Predictors of bleeding after endoscopic mucosal resection of gastric tumors. Gastrointest Endosc 2003; 57: 687-690

[61] Uedo N, Takeuchi Y, Ishihara R, Hanaoka N, Inoue T, Kizu T, Higashino K, Ishii H, Tatsuta M, Chak A, Wong BC. Endoscopic Doppler US for the prevention of ulcer bleeding after endoscopic submucosal dissection for early gastric cancer: a preliminary study (with video). Gastrointest Endosc 2010; 72: 444-448

[62] Choi KD, Jung HY, Lee GH, Oh TH, Jo JY, Song HJ, Hong SS, Kim JH. Application of metal hemoclips for closure of endoscopic mucosal resection-induced ulcers of the stomach to prevent delayed bleeding. Surg Endos 2008; 22: 1882-1886

[63] Fujishiro M, Abe N, Endo M, Kawahara Y, Shimoda R, Nagata S, Homma K, Morita Y, Ueda N. Current management and outcomes of peptic and artificial ulcer bleeding in Japan. Dig Endosc 2010; 22 Suppl 1: S9-14

[64] Villaneuva C, Balanzo J, Torras X, Soriano G, Sainz S, Vilardebell F. Value of second-look endoscopy after injection therapy for bleeding peptic ulcer: a prospective and randomized trial. Gastrointest Endosc 1994; 40: 34-39

[65] Chiu PW, Lam CY, Lee SW, Kwong KH, Lam SH, Lee DT, Kwok SP. Effect of scheduled second therapeutic endoscopy on peptic ulcer rebleeding: a prospective randomised trial. Gut 2003; 52: 1403-1407

[66] Goto O, Fujishiro M, Kodashima S, Ono S, Niimi K, Hirano K, Yamamichi N, Koike K. A second-look endoscopy after endoscopic submucosal dissection for gastric epithelial neoplasm may be unnecessary: a retrospective analysis of postendoscopic submucosal dissection bleeding. Gastrointest
Bleeding and ulcers associated with ESD

Endosc 2010; 71: 241-248

Di Mario F, Battaglia G, Leandro G, Grasso G, Vianello F, Vigneri S. Short-term treatment of gastric ulcer. A meta-analytical evaluation of blind trials. Dig Dis Sci 1996; 41: 1108-1131

Tunis SR, Sheinhait IA, Schmid CH, Bishop DJ, Ross SD. Lansoprazole compared with histamine2-receptor antagonists in healing gastric ulcers: a meta-analysis. Clin Ther 1997; 19: 743-757

Gisbert JP, González L, Calvet X, Roqué M, Gabriel R, Pajares JM. Proton pump inhibitors versus H2-antagonists: a meta-analysis of their efficacy in treating bleeding peptic ulcer. Aliment Pharmacol Ther 2001; 15: 917-926

Goto O, Fujishiro M, Kodashima S, Minatsuki C, Niimi K, Ono S, Yamamichi N, Koike K. Short-term healing process of artificial ulcers after gastric endoscopic submucosal dissection. Gut Liver 2011; 5: 293-297

Kakushima N, Yahagi N, Fujiwara S, Higashino K, Iishi H, Tatsuta M. Effect of a proton pump inhibitor or an H2-receptor antagonist on prevention of bleeding from ulcer after endoscopic submucosal dissection of early gastric cancer: a prospective randomized controlled trial. Am J Gastroenterol 2007; 102: 1610-1616

Asakuma Y, Kudo M, Matsu S, Okada M, Kawasaki M, Umehara Y, Ichikawa T, Kitai S. Comparison of an ecabet sodium and proton pump inhibitor (PPI) combination therapy with PPI alone in the treatment of endoscopic submucosal dissection (ESD)–induced ulcers in early gastric cancer: prospective randomized controlled study. Hepatogastroenterology 2009; 56: 1270-1273

Kato T, Araki H, Onogi F, Ibuka T, Sugiyama A, Tomita E, Nagaki M, Moriwaki H. Clinical trial: rebamipide promotes gastric ulcer healing by proton pump inhibitor after endoscopic submucosal dissection--a randomized controlled study. J Gastroenterol 2010; 45: 285-290

Fujiwara S, Morita Y, Toyonaga T, Kawakami F, Itsho T, Yoshida M, Kutsumi H, Azuma T. A randomized controlled trial of rebamipide plus rabeprazole for the healing of artificial ulcers after endoscopic submucosal dissection. J Gastroenterol 2011; 46: 595-602

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