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EDITORIAL

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

Peer reviewer: David Friedel, MD, Gastroenterology, Winthrop University Hospital, 222 Station Plaza North, Suite 428, Mineola, NY 11501, United States

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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 such as bleeding and gastrointestinal perforation[20-29]. 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[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[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[33,34].

For hemostasis of ESD intraoperative bleeding, Enomoto *et al*[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[36,37]. Therefore, hemostatic forceps, which enable reliable 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[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[40,41]. Moreover, the usefulness not only of monopolar, but also of bipolar hemostatic forceps, has been reported[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%[16]. 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[43]. To predict intraoperative bleeding, identification of the submucosal vascular structure by preoperative endoscopic ultrasonography can be useful[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 (glyceol, 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 *et al*[45] noted that identification of vessels prior to submucosal dissection and prophylactic thermo-coagulation are most important in preventing ESD intraoperative bleeding. Toyonaga *et al*[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[35]. 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 *et al*[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[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[48]. Delayed bleeding often occurs within 24 h postoperatively and is related to lesion location, size, and ulcer-findings[48,55]. For delayed bleeding, in almost all cases, hemostasis is achieved with urgent endoscopic hemostasis[56]. However, cases requiring vascular embolization because endoscopic hemostasis could not be achieved[57], and cases complicated by disseminated intravascular coagulation the day after delayed bleeding[58] have been reported, so caution is necessary.

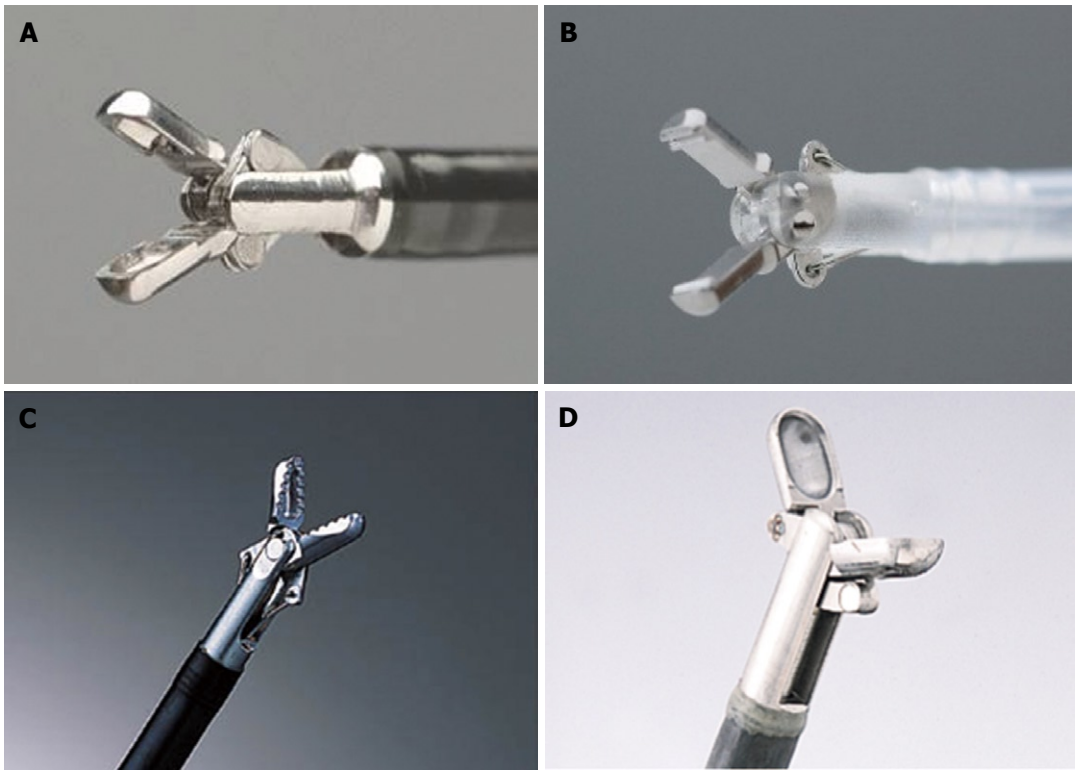

Figure 1 Hemostatic forceps tips. A: Monopolar hemostatic forceps (HDB2422W; Pentax, Tokyo, Japan); B: Bipolar hemostaticforceps (H-S2518; Pentax, Tokyo, Japan); C: Hemostatic forceps (Coagrasper: FD-410LR; Olympus, Tokyo, Japan); D: Hot biopsy forceps (FD-1L-1; Olympus, Tokyo, Japan).

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*[48]	2005	945	6	93
Kakushima *et al*[49]	2006	383	3.4	91
Imagawa *et al*[18]	2006	196	0	93
Onozato *et al*[50]	2006	171	7.6	94
Oka *et al*[16]	2006	195	6.2	83
Hirasaki *et al*[51]	2007	112	7.1	96
Ono *et al*[6]	2008	161	8.7	99
Hoteya *et al*[52]	2009	572	4.9	95
Isomoto *et al*[53]	2009	510	1.8	95
Tsuji *et al*[54]	2010	398	5.8	NA
Akasaka *et al*[28]	2011	1188	3.1	95

NA: Not analyzed.

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*[59], the cause of delayed bleeding is due more to insufficient prophylactic thermo-coagulation than insufficient primary hemostasis during ESD[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*[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*[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[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[64,65]. However, according to Goto *et al*[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, compared to ulcers located in the upper and middle third of the stomach, because delayed bleeding occurs earlier, careful follow-up observation or early second-look endoscopy may be useful[54,66].

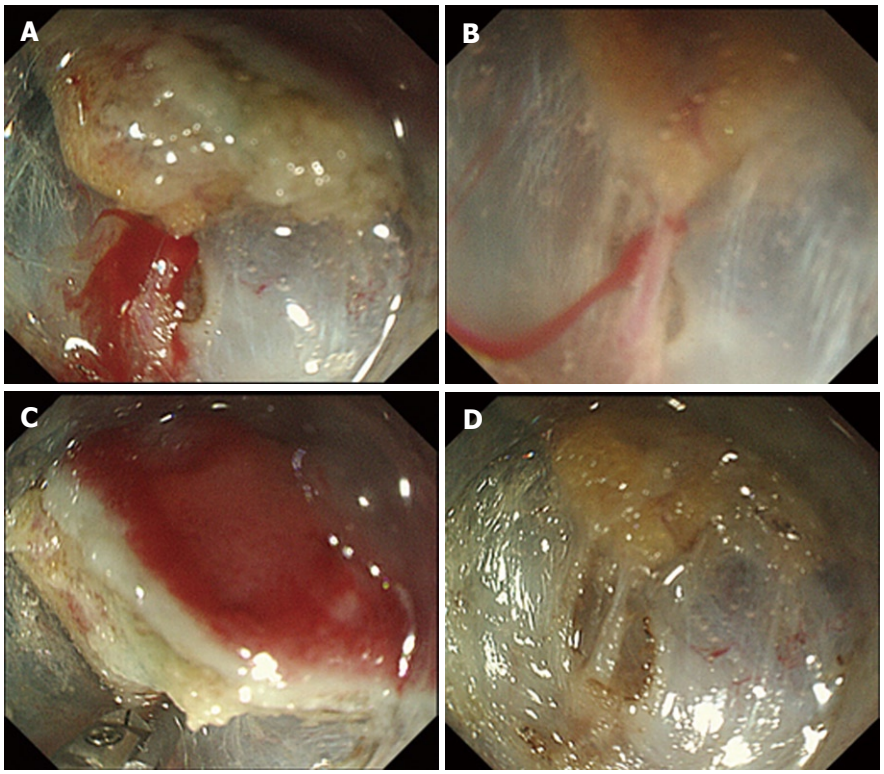

Figure 2 Hemostatic procedure for endoscopic submucosal dissectionintraoperative bleeding using hemostatic forceps. A: Pulsatile bleeding is observed during submucosal dissection; B: By filling the tip attachment with water, the bleeding point can be pinpointed and identified; C: After identifying the bleeding point, the vessel is securely grasped by hemostatic forceps, and thermo-coagulation is performed; D: Complete hemostasis is achieved, without excessive coagulation.

MANAGEMENT OF ARTIFICAL 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, *Helicobacterpylori* 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 antiulcer 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

Table 2 Healing process of gastric artificial ulcers after endoscopic submucosal dissection

Author	Year	Total cases	Drugs administration	Weeks	Ulcer healing rate (%)		Average ulcer size	
					4 wk	8 wk	Maximal diameter (mm)	Resected area (mm^2)
Kakushima *et al*[71]	2004	70	PPI + sucralfate	8	NA	100	34.7	NA
Lee *et al*[76]	2004	26	OPZ 20 mg	1	12	NA	NA	503
		34	OPZ 20 mg	4	15	NA	NA	575
Yamaguchi *et al*[78]	2005	29	OPZ 20 mg	8	NA	NA	27.8	NA
		28	Famotidine 40 mg	8	NA	NA	22.4	NA
Uedo *et al*[79]	2007	73	RPZ 20 mg	8	NA	83	41	NA
		70	Cimetidinde 800 mg	8	NA	89	40.5	NA
Asakuma *et al*[80]	2009	28	RPZ 20 mg + ES 3.0 g	8	40.7	96.3	NA	1306
		28	RPZ 20 mg	8	11.5	76.9	NA	1274
Kato *et al*[81]	2010	31	RPZ 10 mg + rebamipide 300 mg	4	68	NA	35	NA
		31	RPZ 10 mg	4	35	NA	31	NA
Fujiwara *et al*[82]	2011	30	RPZ 20 mg + rebamipide 300 mg	8	NA	86.7	41	1453
		31	RPZ 20 mg	8	NA	54.8	42.8	1521
Niimi *et al*[77]	2011	55	RPZ 10 mg	2	NA	80.0	32.7	NA

NA: Not analyzed; PPI: Proton pump inhibitor; OPZ: Omeprazole; RPZ: Rabeprazole; ES: Ecabet sodium.

in the ulcer healing process may be low.

Yamaguchi *et al*[78] 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*[79] 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*[80] compared combined therapy with a PPI (rabeprazole 20 mg/d) and ecabet 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*[81] 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, Fujiwara *et al*[82] 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 H, Gotoda T, Shirao 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 **Ohkuwa M**, Hosokawa K, Boku N, Ohtu A, Tajiri H, Yoshida S. New endoscopic treatment for intramucosal 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**, Hasuike N, Inui T, Takizawa K, Ikehara H, Yamaguchi Y, Otake Y, Matsubayashi H. Usefulness of a novel electrosurgical 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 en-bloc resection of large superficial tumors in the stomach and colon using sodium hyaluronate and small-caliber-tip transparent hood. *Endoscopy* 2003; **35**: 690-694
9 **Inoue H**, Kudo S. A novel procedure of en block EMR using triangle-tipped knife (abstract). *Gastrointest Endosc* 2003; **57**: AB86
10 **Yahagi N**, Fujishiro M, Kakushima N, Kobayashi K, Hashimoto T, Oka M, Iguchi M, 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, Yamamichi 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**: 688-694
13 **Toyonaga T**, Nishino E, Dozaiku 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 en 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 scissor forceps for early gastrointestinal tract neoplasms. *World J Gastrointest Endosc* 2010; **2**: 90-96
16 **Oka S**, Tanaka S, Kaneko I, Mouri 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, Iwakiri 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 neoplasms. *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, Hasuike 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 Hepatol* 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 of gastric tumors. *Endoscopy* 2010; **42**: 441-447
28 **Akasaka T**, Nishida T, Tsutsui S, Michida T, Yamada T, Ogiyama H, Kitamura S, Ichiba M, Komori M, Nishiyama O, Nakanishi F, Zushi S, Nishihara A, Iijima H, Tsujii 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**: 73-77
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, Ishii 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, Matthewson 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*

2006; **16**: 137-140
35 **Enomoto S**, Yahagi N, Fujishiro M, Oka M, Kakushima N, Iguchi M, Yanaoka K, Arii 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, Maekita T, Magari H, Mukoubayashi C, Nakazawa K, Iguchi M, Yanaoka K, Arii K, Tamai H, Omata M, Ichinose M. Assessment of intraoperative bleeding during endoscopic submucosal dissection and endoscopic hemostasis using high-frequency hemostatic forceps. *J Wakayama Med* 2009; **60**: 124-129
38 **Fujishiro M**, Abe N, Endo M, Kawahara Y, Shimoda R, Nagata S, Homma K, Morita Y, Uedo 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 **Coumaros 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 **Hirao M**, Masuda K, Asanuma T, Naka H, Noda K, Matsuura 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, Matsui 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: S128-130
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: S123-127
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: S119-122
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 **Hirasaki S**, Kanzaki 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 **Isomoto 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**, Ohata K, 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**: 2913-2917
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 IK, 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**, Hajiro 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, Iishi H, Tatsuta M, Chak A, Wong RC. 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 Endosc* 2008; **22**: 1882-1886
63 **Fujishiro M**, Abe N, Endo M, Kawahara Y, Shimoda R, Nagata S, Homma K, Morita Y, Uedo N. Current managements and outcomes of peptic and artificial ulcer bleeding in Japan. *Dig Endosc* 2010; **22** Suppl 1: S9-14
64 **Villanueva C**, Balanzó J, Torras X, Soriano G, Sáinz S, Vilardell 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*

Endosc 2010; **71**: 241-248
67 **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
68 **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
69 **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
70 **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
71 **Kakushima N**, Yahagi N, Fujishiro M, Iguchi M, Oka M, Kobayashi K, Hashimoto T, Omata M. The healing process of gastric artificial ulcers after endoscopic submucosal dissection. *Dig Endosc* 2004; **16**: 327-331
72 **Kakushima N**, Fujishiro M, Yahagi N, Kodashima S, Nakamura M, Omata M. Helicobacter pylori status and the extent of gastric atrophy do not affect ulcer healing after endoscopic submucosal dissection. *J Gastroenterol Hepatol* 2006; **21**: 1586-1589
73 **Kakushima N**, Fujishiro M, Kodashima S, Kobayashi K, Tateishi A, Iguchi M, Imagawa A, Motoi T, Yahagi N, Omata M. Histopathologic characteristics of gastric ulcers created by endoscopic submucosal dissection. *Endoscopy* 2006; **38**: 412-415
74 **Huang Y**, Kakushima N, Takizawa K, Tanaka M, Ikehara H, Yamaguchi Y, Matsubayashi H, Ono H, Oishi T, Nakajima T. Risk factors for recurrence of artificial gastric ulcers after endoscopic submucosal dissection. *Endoscopy* 2011; **43**: 236-239
75 **Oh TH**, Jung HY, Choi KD, Lee GH, Song HJ, Choi KS, Chung JW, Byeon JS, Myung SJ, Yang SK, Kim JH. Degree of healing and healing-associated factors of endoscopic submucosal dissection-induced ulcers after pantoprazole therapy for 4 weeks. *Dig Dis Sci* 2009; **54**: 1494-1499
76 **Lee SY**, Kim JJ, Lee JH, Kim YH, Rhee PL, Paik SW, Rhee JC. Healing rate of EMR-induced ulcer in relation to the duration of treatment with omeprazole. *Gastrointest Endosc* 2004; **60**: 213-217
77 **Niimi K**, Fujishiro M, Goto O, Kodashima S, Minatsuki C, Hirayama I, Mochizuki S, Ono S, Yamamichi N, Kakushima N, Ichinose M, Koike K. Prospective single-arm trial of two-week rabeprazole treatment for ulcer healing after gastric endoscopic submucosal dissection.*Dig Endosc* 2011; In press
78 **Yamaguchi Y**, Katsumi N, Tauchi M, Toki M, Nakamura K, Aoki K, Morita Y, Miura M, Morozumi K, Ishida H, Takahashi S. A prospective randomized trial of either famotidine or omeprazole for the prevention of bleeding after endoscopic mucosal resection and the healing of endoscopic mucosal resection-induced ulceration. *Aliment Pharmacol Ther* 2005; **21** Suppl 2: 111-115
79 **Uedo N**, Takeuchi Y, Yamada T, Ishihara R, Ogiyama H, Yamamoto S, Kato M, Tatsumi K, Masuda E, Tamai C, Yamamoto 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
80 **Asakuma Y**, Kudo M, Matsui 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 study. *Hepatogastroenterology* 2009; **56**: 1270-1273
81 **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
82 **Fujiwara S**, Morita Y, Toyonaga T, Kawakami F, Itoh 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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TOPIC HIGHLIGHT

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Esophageal squamous cell carcinoma - precursor lesions and early diagnosis

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Abstract

Squamous cell carcinoma of the esophagus (SCCE) carries a poor prognosis due to late diagnosis. Early detection is highly desirable, since surgical and endoscopic resection offers the only possible cure for esophageal cancer. Population screening should be undertaken in high risk areas, and in low or moderate risk areas for people with risk factors (alcoholics, smokers, mate drinkers, history of head and neck cancer, achalasia and lye stricture of the esophagus). Esophageal balloon cytology is an easy and inexpensive sampling technique, but the current methods are insufficient for primary screening due to sampling errors. Conventional endoscopy with biopsy remains the standard procedure for the identification of pre-malignant and early malignant changes in esophageal mucosa and endoscopic detection. It may be enhanced by several techniques such as dye and optic chromoendoscopy, magnifying endoscopy, and optical-based spectroscopic and imaging modalities. Since more than 80% of SCCE deaths occur in developing countries, where expensive techniques such as narrow band imaging (NBI) and autofluorescence imaging are unavailable, the most cost-effective tool for targeting biopsies may be Lugol dye chromoendoscopy, since it is easy, accurate, inexpensive and available worldwide. In ideal conditions, or in developed countries, is it reasonable to think that optimal detection will require a combination of techniques, such as the combination of Lugol' s chromoendoscopy and NBI to identify esophageal areas that require further characterization by a high resolution technique. The efficacy and cost-effectiveness will determine whether these modalities will become part of standard endoscopy practice.

Key words: Autofluorescence endoscopy; Early diagnosis; Esophageal cancer; Esophageal squamous cell carcinoma; Lugol's solution; Narrow-band imaging endoscopy

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INTRODUCTION

The cancers arising from the esophageal mucosa, including squamous cell carcinoma (SCCE) and adenocarcino-

ma (ADC), are the eighth most common cancers worldwide, with 482 000 new cases estimated in 2008, and are the sixth most common cause of death from cancer with 4 070 00 deaths in the same year[1]. The majority of new cases occur in developing countries accounting for 83% of cases and 86% of deaths, with incidence ratios varying 16-fold between high incidence regions, such as Southern and Eastern Africa and Eastern Asia, and low incidence regions like Western and Middle Africa and Central America[2]. SCCE is still the most frequent histological type worldwide, even after the 400% increase in the prevalence of ADC in the United States[3,4] and in some countries in Western Europe[5,6] where ADC accounts for more than 80% of new cases[7]. Indeed, the predominance of SCCE is due to its high prevalence in Eastern Asia, as it is observed in some provinces of China, Turkey and Iran, where as much as 120 to 175 new cases are diagnosed per 100 000 inhabitants each year[8]. Intermediate prevalence of SCCE has been observed in France[6], Southern and Eastern Africa[9], and in some countries of South America such as Uruguay, southeast Argentina and southern Brazil, where SCCE still accounts for more than 80% of esophageal cancers[10].

Esophageal cancers carry a high mortality mainly due to its late diagnosis, with a five-year survival of less than 10%[11]. More than 70% of diagnosis are made in patients presenting with dysphagia and weight loss, clinical findings frequently observed in patients in at least stage Ⅱ disease[12,13]. In developing countries more than 90% of diagnosis of esophageal cancers are at stage Ⅱ to Ⅳ with only 15% to 30% of patients elected for curative surgery[14]. Early diagnosis is uncommon even in developed countries such as France, Japan and the United States, where stage I accounts for just 4% to 25% of new diagnosis[13,15]. This negatively affects the 3- and 5-year survival of patients submitted to multimodality treatments, reaching between 8% to 40% and 5% to 15%, respectively[16]. Diagnosis of early stage lesions is still the best way to improve the chances of cure and survival.

The heterogeneity of risk factors, the differences in geographic distribution and the ethnic groups at risk, make it really difficult to rely on serologic markers for the diagnosis of SCCE. Some attempts have been made, but none of them can be used in clinical practice, due to their low sensitivity[17] or lack of confirmatory values for the diagnosis of early SCCE[18-21]. Since serologic tests are not clinically available yet, more invasive tests are still needed to diagnose SCCE.

Therefore, the aim of the current article is to review some of the most recent efforts that have been made to enhance early diagnosis of SCCE and its precursor lesions.

DEFINITION OF EARLY DIAGNOSIS

Invasive SCCE develops from intraepithelial neoplasia, such as dysplasia and carcinoma *in situ*, that reaches the lamina propria and extends beyond the submucosa[22]. In a recent Italian study by Ancona and colleagues[23], patients with lesions that were restricted to the esophageal mucosa did not present lymph node metastasis, while lymph node metastasis were observed in 8.3% of patients with tumors restricted to the first third of the submucosa (Sm1). In fact, the diagnosis and treatment of such early stage lesions can improve the survival rates of SCCE, reaching a five-year survival rate of more than 90% after endoscopic or surgical treatment[24].

For the purpose of this review, early esophageal SCCE will be considered high-grade dysplasia, carcinoma in situ, and tumors limited to the upper two thirds of the submucosa. These three types of lesions have a low rate of lymph node metastasis and present higher rates of cure and survival.

RISK FACTORS – WHO SHOULD BE SCREENED?

Early diagnosis of SCCE must not be based on symptoms, since they occur frequently in advanced disease, consequently, screening techniques must be used in asymptomatic individuals exposed to risk factors.

In high risk areas of the "esophageal cancer belt", such as northern Iran, some provinces of north-central China and north Afghanistan, the main risk factors are poor nutritional and socioeconomic status[25,26], exposure to polycyclic aromatic hydrocarbons (PAH)[27-30], low intake of vegetables and fruits[31], drinking hot beverages[32,33] and there is probably a role for genetic factors[34,35]. These risk factors affect the whole population in these high risk areas, and screening of SCCE in these populations must include the largest number of people that live in these places, with lower costs and less invasive devices.

In moderate and lower risk Western countries, the most important risk factors are the combination of tobacco smoking and excessive alcohol consumption[36-44]. A previous diagnosis of head and neck squamous cell carcinoma has been observed to have a significant impact on the incidence of SCCE[45-47]. Some areas of South America, such as southern Brazil, Uruguay, Paraguay and northwestern Argentina, have a moderate prevalence of SCCE which is influenced by ingestion of a hot beverage called *maté*. This hot beverage is an infusion of the leaves of Ilex paraguayensis that probably increases the risk of SCCE due to its high temperature[33,38,48-51] and its high content of PAH[52,53]. Some other risk factors that may contribute to SCCE are achalasia, previous radiotherapy for breast cancer, previous caustic injury to the esophagus and thylosis. SCCE screening in moderate and lower risk Western countries must be carried out in subjects exposed to the risk factors described above[54].

CYTOLOGICAL SCREEENING

In the late 1950s a new technique was developed in China to collect cells from the esophageal mucosa uti-

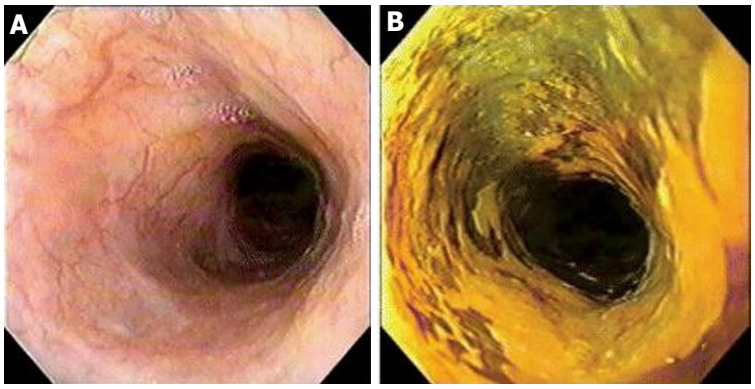

Figure 1 Conventional esophagoscopy and Lugol's chromoendoscopy. A: Conventional esophagoscopy presenting normal appearing mucosa; B: Lugol's chromoendoscopy disclosed an unstained areaafter multiple biopsies, the diagnosis was high-grade dysplasia.

lizing an inflatable balloon covered with a cotton web attached to the tip of a plastic catheter[55]. This device was swallowed and passed down the esophagus to the gastric cardia with the balloon deflated. Once it reached the gastric cardia, the balloon was inflated with air using a 20mL syringe attached to the proximal end of the catheter, and the inflated balloon was gently withdrawn until it reached the upper esophageal sphincter, deflated and then completely withdrawn. The "Chinese Balloon" was designed to be used in multiple patients after simple washing techniques. Other rubber and mechanical disposable balloons and other devices such as sponges have been developed and used in several studies conducted in China which reported that exfoliative cytology may allow early diagnosis of SCCE[55-59].

After collecting squamous cells using this method, slides are stained by the Papanicolaou technique and analyzed. Cytologic findings of atypical squamous cells of undetermined significance (ASCUS), low grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL) and carcinoma according to the Bethesda system for squamous cells[60] must undergo upper digestive endoscopy to determine the presence of SCCE.

Many studies in China and one study in Brazil have shown that exfoliative cytology is a good way to collect squamous cells from the esophagus, however, the results of conventional cytology in the diagnosis of SCCE has been discouraging with sensitivities between 39% and 66%[56-59,61-63].

Cytological samples collected using the methods described above are representative of the esophageal mucosa and it is possible that a molecular marker could increase the sensitivity of this inexpensive and simple technique. Immunocytochemical expression of p53 protein was tested recently in southern Brazil, but did not improve the yield of cytological analyses[64]. Two studies have been conducted in China to detect molecular markers that could increase the sensitivity and specificity of balloon cytology[65,66]. One of these studies, published by Adams and colleagues[65], evaluated the presence of methylation in eight genes in esophageal balloon cytology specimens from 147 patients with endoscopic biopsy diagnoses ranging from normal mucosa through to severe squamous dysplasia. This study suggested that evaluation of gene methylation in cytological samples may have utility for the early detection of esophageal squamous dysplasia and early SCCE, however, more sensitive methylation markers will be required for clinical use. The second study by McGruder and colleages[66] tested the telomerase activity measured by real time PCR in esophageal balloon samples in 8 patients from China, and the results seemed to enhance the accuracy of the cytological analysis, however, larger populations and different ethnic groups should be tested before this technique is used in clinical practice.

LUGOL'S DYE CHROMOENDOSCOPY – AN INEXPENSIVE AND SIMPLE SCREENING METHOD

Due to the low sensitivity of conventional endoscopy for the diagnosis of early SCCE[67], new methods were required to evaluate the esophageal mucosa of high risk patients. During the 1990s, multiple reports on Lugol' s dye chromoendoscopy were published and showed how easy, inexpensive and sensitive this method was for detecting early and late squamous cell neoplasia[68-70]. It is based on the lack of absorption of the iodine stain by abnormal squamous tissue, such as inflamed, dysplastic or neoplastic lesions. The esophageal mucosa evaluation occurs during conventional endoscopy, when 10mL to 40 mL of 0.5% to 3% Lugol's solution is sprayed onto the esophageal mucosa which results in a green-brown, dark-brown, or black discoloration of normal mucosa lasting up to 5 to 8 min (Figure 1). Absence of staining indicates abnormal mucosa that can be biopsied. Lesions with a diameter smaller than 0.5 cm rarely show neoplastic lesions[46].

One of the first reports of Lugol's dye chromoendoscopy was published by Misumi and colleagues in 1990[71] and demonstrated that this method could reveal esophageal cancer in normal appearing mucosa under conventional endoscopy. Since then, many studies have been published and the use of this method has increased worldwide. Of great interest is a study conducted in China by Dawsey *et al*[68], where the method showed great sensitivity in revealing early and late SCCE in a high risk population in Linxian province. The same study showed that iodine staining improved the visualization of the lateral margins of the lesions, which was important in

guiding endoscopic biopsies and treatment.

Lugol staining of the esophagus has been used in different populations. Studies from Japan and from Brazil which examined alcoholic patients confirmed the significant sensitivity of this chromoendoscopic method when compared with conventional endoscopy[69,72-74]. Patients with previous head and neck cancers were evaluated and similar results were obtained[46,47,75].

The largest series on the use of Lugol's chromoendoscopy was a multicenter study from France published in 2006 by Dubuc and colleagues[15]. This French study evaluated 1095 patients divided into 4 groups according to exposure to risk factors to SCCE as follows: group 1 –patients with previous diagnosis of head and neck or tracheobronchial squamous cell carcinoma; group 2 –patients with alcoholic pancreatitis; group 3 - patients with alcoholic cirrhosis; group 4 - alcohol and tobacco addicts. SCCE and/or dysplasia were observed in 9.9%, 0%, 7.3% and 2.9% in these groups, respectively. Conventional endoscopy detected only 35 esophageal lesions in these patients, while Lugol staining chromoendoscopy detected 67. The difference in diagnostic accuracy was more important for early lesions like low-grade dysplasia, since 77% of these lesions were observed only after spraying of the iodine dye. According to the authors, Lugol's chromoendoscopy must be used for SCCE screening of patients with previous head and neck or tracheobronchial squamous cell carcinoma.

The pitfalls in its use include increased duration of the procedure, the risk of allergic reactions to the iodine solution and chest pain in some patients[68,70]. The duration of endoscopy is between 5 min and 10 min longer than conventional endoscopy[68,70]. Chest pain and agitation during endoscopy are uncommon, and when they do occur they are easily managed. Indeed, these problems have been surpassed by the advantages of this simple, inexpensive, worldwide available and accurate method for diagnosing early squamous dysplasia and SCCE, when compared to conventional endoscopy[15,46,47,68-72,74-76] and esophageal capsule endoscopy[77].

NARROW-BAND IMAGING – A PROMISING OPTIC-BASED CHROMOENDOSCOPY

Narrow-band imaging (NBI) is a novel, noninvasive optical technique that uses reflected light to visualize the organ surface, and works as an optic-based chromoendoscopic method to detect early lesions[78]. A single-touch of the control knob on the grip of the endoscope allows switching from the standard endoscopy to the NBI filter, emphasizing capillary vessels in the endoscopic images, with image processing in real time[79], and identifying early squamous cell lesions as brownish, well demarcated lesions[80]. NBI when used without magnification has high sensitivity, but a high rate of false-positive lesions, with results similar to Lugol's chromoendoscopy[81].

Adding magnification to NBI increased the sensitivity and the specificity for the screening of early lesions due to identification of intraepithelial papillary loop (IPCL) patterns such as dilatation, tortuosity, caliber change and variety in shape suggestive of mucosal high-grade neoplasia as shown by Yoshida *et al*[79]. Ishihara and colleagues[82] identified, in a multivariate analysis, that brownish epithelium and brownish dots were independent factors for the identification of early squamous neoplastic lesions, with an odds ratio of 25.5 [95% confidence interval (CI): 2.4–268] for brownish epithelium and 19.3 (95% CI: 1.8–207.7) for brownish dots. Brownish epithelium and brownish dots had a moderate interobserver agreement in this study. In the same study, IPCL patterns such as dilatation, tortuosity, caliber change and variety in shape were not associated with high-grade dysplasia.

As for Lugol's chromoendoscopy, the majority of studies on NBI have been conducted in previous head and neck cancer patients. The results are impressive with a sensitivity greater than 90% in this population[80,81,83,84]. However, some pitfalls must be outlined: (1) endoscopes with the NBI system are more expensive than conventional endoscopes and Lugol's solution; and (2) the NBI technique requires expertise for application. Ishihara and colleagues[85], showed that NBI, when used by less experienced endoscopists, had a sensitivity of 53% in diagnosing high-grade dysplasia.

AUTOFLUORESCENCE IMAGING – AN OPTIC-BASED CHROMOENDOSCOPY FOR MULTIMODALITY APPROACH

Autofluorescence imaging (AFI) is another optic-based chromoendoscopic device designed to detect early lesions. AFI neoplastic areas, that usually involve a thickening of the mucosal layer and increased hemoglobin, emit weaker autofluorescence compared to non-neoplastic areas. In this technique, non-neoplastic areas appear green in color, whereas neoplastic areas are purple or magenta. Some studies have been conducted in the screening of early squamous esophageal lesions and showed that AFI had a higher sensitivity than white-light endoscopy to detect superficial lesions (79% *vs* 51%, respectively), however, its accuracy was worse than Lugol's chromoendoscopy or NBI[86,87].

CONCLUSION

Esophageal cancer is a common malignancy with a very poor prognosis. It represents a challenge in medical practice and in the field of public health. It is a devastating disease that continues to have a 5-year survival of less than 10% despite the advances in multimodality therapy. Since surgical and endoscopic resection offer the only possible cure for esophageal cancer, early detection via screening is appealing, particularly in high risk populations. However, so far, there are no guidelines for the screening of SCCE.

Esophageal balloon cytology is a patient-acceptable sampling technique, but the current methods are insufficient for primary screening due to sampling errors. Blind sampling of a large organ misses small lesions and morphologic evaluation of a small percentage of the cell sample misses rare abnormal cells. Molecular markers may be able to help, but the use of biomarkers has to wait for its validation and availability.

Currently there is no single test or testing series that screen for SCCE in a reliable and cost-effective manner, and conventional white light endoscopy with biopsy remains the standard procedure for the identification of pre-malignant and early malignant changes in esophageal mucosa. Endoscopic detection may be enhanced by several techniques such as dye and optic chromoendoscopy, magnifying endoscopy, and optical-based spectroscopic and imaging modalities.

Considering that esophageal cancer is a highly lethal disease, with about 80% of deaths occurring in developing countries, the most efficient and cost-effective tool for targeting biopsies may be Lugol dye chromoendoscopy, since it is an easy, accurate, inexpensive and worldwide available endoscopic technique. In areas of medium and low risk, individual cases should be considered for screening only if the risk and costs to the individual warrant aggressive screening and follow-up evaluation, such as in certain groups of subjects at high risk of the disease such as alcoholics, smokers, *mate* drinkers, previous head and neck cancer, achalasia and lye stricture of the esophagus.

In ideal conditions, or in developed countries where expensive techniques such as NBI and AFI are available, it is reasonable to think that optimal detection will require a combination of techniques. For example, a suspicious area could be identified initially by NBI or Lugol' s chromoendoscopy, and then further characterized by a high resolution technique, such as confocal endoscopy. The diagnostic performance, availability and cost-effectiveness will determine whether these modalities will become part of standard endoscopy practice.

REFERENCES

1 **Ferlay J**, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**: 2893-2917
2 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2010; **61**: 69-90
3 **Brown LM**, Devesa SS, Chow WH. Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age. *J Natl Cancer Inst* 2008; **100**: 1184-1187
4 **Cook MB**, Chow WH, Devesa SS. Oesophageal cancer incidence in the United States by race, sex, and histologic type, 1977-2005. *Br J Cancer* 2009; **101**: 855-859
5 **Orengo MA**, Casella C, Fontana V, Filiberti R, Conio M, Rosso S, Tumino R, Crosignani P, De Lisi V, Falcini F, Vercelli M. Trends in incidence rates of oesophagus and gastric cancer in Italy by subsite and histology, 1986-1997. *Eur J Gastroenterol Hepatol* 2006; **18**: 739-746
6 **Bosetti C**, Levi F, Ferlay J, Garavello W, Lucchini F, Bertuccio P, Negri E, La Vecchia C. Trends in oesophageal cancer incidence and mortality in Europe. *Int J Cancer* 2008; **122**: 1118-1129
7 **Cross AJ**, Freedman ND, Ren J, Ward MH, Hollenbeck AR, Schatzkin A, Sinha R, Abnet CC. Meat consumption and risk of esophageal and gastric cancer in a large prospective study. *Am J Gastroenterol* 2011; **106**: 432-442
8 **Gholipour C**, Shalchi RA, Abbasi M. A histopathological study of esophageal cancer on the western side of the Caspian littoral from 1994 to 2003. *Dis Esophagus* 2008; **21**: 322-327
9 **Wakhisi J**, Patel K, Buziba N, Rotich J. Esophageal cancer in north rift valley of Western Kenya. *Afr Health Sci* 2005; **5**: 157-163
10 **de Barros SG**, Vidal RM, Luz LP, Ghisolfi ES, Barlem GG, Komlós F, Wolff FH, Breyer HP, Pütten AC, Dietz J, Kruel CD, Grüber AC, Prolla JC. [Prevalence of adenocarcinoma of the esophagus and esophagogastric junction in a 10 year period at a cancer referral center in southern Brazil]. *Arq Gastroenterol* 1999; **36**: 32-36
11 CRUK 2009 'Cancer survival rates for patients diagnosed 1996-1999.' Survival statistics for the most common cancers. Cited 23/05/2011. Available from: URL: http: //info.cancerresearchuk.org/cancerstats/survival/latestrates/
12 **Daly JM**, Fry WA, Little AG, Winchester DP, McKee RF, Stewart AK, Fremgen AM. Esophageal cancer: results of an American College of Surgeons Patient Care Evaluation Study. *J Am Coll Surg* 2000; **190**: 562-72; discussion 572-573
13 **Schlansky B**, Dimarino AJ, Loren D, Infantolino A, Kowalski T, Cohen S. A survey of oesophageal cancer: pathology, stage and clinical presentation. *Aliment Pharmacol Ther* 2006; **23**: 587-593
14 **Abdullah M**, Karim AA, Goh KL. Late presentation of esophageal cancer: observations in a multiracial South-East Asian population. *J Dig Dis* 2010; **11**: 28-33
15 **Dubuc J**, Legoux JL, Winnock M, Seyrig JA, Barbier JP, Barrioz T, Laugier R, Boulay G, Grasset D, Sautereau D, Grigoresco D, Butel J, Scoazec JY, Ponchon T. Endoscopic screening for esophageal squamous-cell carcinoma in high-risk patients: a prospective study conducted in 62 French endoscopy centers. *Endoscopy* 2006; **38**: 690-695
16 **Allum WH**, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. *J Clin Oncol* 2009; **27**: 5062-5067
17 **Chen W**, Abnet CC, Wei WQ, Roth MJ, Lu N, Taylor PR, Pan QJ, Luo XM, Dawsey SM, Qiao YL. Serum markers as predictors of esophageal squamous dysplasia and early cancer. *Anticancer Res* 2004; **24**: 3245-3249
18 **Liu WL**, Zhang G, Wang JY, Cao JY, Guo XZ, Xu LH, Li MZ, Song LB, Huang WL, Zeng MS. Proteomics-based identification of autoantibody against CDC25B as a novel serum marker in esophageal squamous cell carcinoma. *Biochem Biophys Res Commun* 2008; **375**: 440-445
19 **Tomita H**, Ichikawa D, Ikoma D, Sai S, Tani N, Ikoma H, Fujiwara H, Kikuchi S, Okamoto K, Ochiai T, Otsuji E. Quantification of circulating plasma DNA fragments as tumor markers in patients with esophageal cancer. *Anticancer Res* 2007; **27**: 2737-2741
20 **Ikoma D**, Ichikawa D, Ueda Y, Tani N, Tomita H, Sai S, Kikuchi S, Fujiwara H, Otsuji E, Yamagishi H. Circulating tumor cells and aberrant methylation as tumor markers in patients with esophageal cancer. *Anticancer Res* 2007; **27**: 535-539
21 **Wu IC**, Wu DC, Huang CC, Lin HS, Chen YK, Tsai HJ, Lu CY, Chou SH, Chou YP, Li LH, Tai SY, Wu MT. Plasma decorin predicts the presence of esophageal squamous cell carcinoma. *Int J Cancer* 2010; **127**: 2138-2146
22 **Wang GQ**, Abnet CC, Shen Q, Lewin KJ, Sun XD, Roth MJ, Qiao YL, Mark SD, Dong ZW, Taylor PR, Dawsey SM. Histological precursors of oesophageal squamous cell carcinoma: results from a 13 year prospective follow up study in a high risk population. *Gut* 2005; **54**: 187-192

23 **Ancona E**, Rampado S, Cassaro M, Battaglia G, Ruol A, Castoro C, Portale G, Cavallin F, Rugge M. Prediction of lymph node status in superficial esophageal carcinoma. *Ann Surg Oncol* 2008; **15**: 3278-3288

24 **Shimizu Y**, Tsukagoshi H, Fujita M, Hosokawa M, Kato M, Asaka M. Long-term outcome after endoscopic mucosal resection in patients with esophageal squamous cell carcinoma invading the muscularis mucosae or deeper. *Gastrointest Endosc* 2002; **56**: 387-390

25 **Abnet CC**, Kamangar F, Islami F, Nasrollahzadeh D, Brennan P, Aghcheli K, Merat S, Pourshams A, Marjani HA, Ebadati A, Sotoudeh M, Boffetta P, Malekzadeh R, Dawsey SM. Tooth loss and lack of regular oral hygiene are associated with higher risk of esophageal squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 2008; **17**: 3062-3068

26 **Islami F**, Kamangar F, Nasrollahzadeh D, Aghcheli K, Sotoudeh M, Abedi-Ardekani B, Merat S, Nasseri-Moghaddam S, Semnani S, Sepehr A, Wakefield J, Møller H, Abnet CC, Dawsey SM, Boffetta P, Malekzadeh R. Socio-economic status and oesophageal cancer: results from a population-based case-control study in a high-risk area. *Int J Epidemiol* 2009; **38**: 978-988

27 **Roth MJ**, Strickland KL, Wang GQ, Rothman N, Greenberg A, Dawsey SM. High levels of carcinogenic polycyclic aromatic hydrocarbons present within food from Linxian, China may contribute to that region's high incidence of oesophageal cancer. *Eur J Cancer* 1998; **34**: 757-758

28 **Wornat MJ**, Ledesma EB, Sandrowitz AK, Roth MJ, Dawsey SM, Qiao YL, Chen W. Polycyclic aromatic hydrocarbons identified in soot extracts from domestic coal-burning stoves of Henan Province, China. *Environ Sci Technol* 2001; **35**: 1943-1952

29 **Abedi-Ardekani B**, Kamangar F, Hewitt SM, Hainaut P, Sotoudeh M, Abnet CC, Taylor PR, Boffetta P, Malekzadeh R, Dawsey SM. Polycyclic aromatic hydrocarbon exposure in oesophageal tissue and risk of oesophageal squamous cell carcinoma in north-eastern Iran. *Gut* 2010; **59**: 1178-1183

30 **Kamangar F**, Strickland PT, Pourshams A, Malekzadeh R, Boffetta P, Roth MJ, Abnet CC, Saadatian-Elahi M, Rakhshani N, Brennan P, Etemadi A, Dawsey SM. High exposure to polycyclic aromatic hydrocarbons may contribute to high risk of esophageal cancer in northeastern Iran. *Anticancer Res* 2005; **25**: 425-428

31 **Zou XN**, Taylor PR, Mark SD, Chao A, Wang W, Dawsey SM, Wu YP, Qiao YL, Zheng SF. Seasonal variation of food consumption and selected nutrient intake in Linxian, a high risk area for esophageal cancer in China. *Int J Vitam Nutr Res* 2002; **72**: 375-382

32 **Islami F**, Pourshams A, Nasrollahzadeh D, Kamangar F, Fahimi S, Shakeri R, Abedi-Ardekani B, Merat S, Vahedi H, Semnani S, Abnet CC, Brennan P, Møller H, Saidi F, Dawsey SM, Malekzadeh R, Boffetta P. Tea drinking habits and oesophageal cancer in a high risk area in northern Iran: population based case-control study. *BMJ* 2009; **338**: b929

33 **Islami F**, Boffetta P, Ren JS, Pedoeim L, Khatib D, Kamangar F. High-temperature beverages and foods and esophageal cancer risk--a systematic review. *Int J Cancer* 2009; **125**: 491-524

34 **Akbari MR**, Malekzadeh R, Nasrollahzadeh D, Amanian D, Sun P, Islami F, Sotoudeh M, Semnani S, Boffeta P, Dawsey SM, Ghadirian P, Narod SA. Familial risks of esophageal cancer among the Turkmen population of the Caspian littoral of Iran. *Int J Cancer* 2006; **119**: 1047-1051

35 **An JY**, Fan ZM, Gao SS, Zhuang ZH, Qin YR, Li JL, He X, Tsao GS, Wang LD. Loss of heterozygosity in multistage carcinogenesis of esophageal carcinoma at high-incidence area in Henan Province, China. *World J Gastroenterol* 2005; **11**: 2055-2060

36 **Brown LM**, Hoover R, Silverman D, Baris D, Hayes R, Swanson GM, Schoenberg J, Greenberg R, Liff J, Schwartz A, Dosemeci M, Pottern L, Fraumeni JF. Excess incidence of squamous cell esophageal cancer among US Black men: role of social class and other risk factors. *Am J Epidemiol* 2001; **153**: 114-122

37 **Castellsagué X**, Muñoz N, De Stefani E, Victora CG, Castelletto R, Rolón PA, Quintana MJ. Independent and joint effects of tobacco smoking and alcohol drinking on the risk of esophageal cancer in men and women. *Int J Cancer* 1999; **82**: 657-664

38 **De Stefani E**, Muñoz N, Estève J, Vasallo A, Victora CG, Teuchmann S. Mate drinking, alcohol, tobacco, diet, and esophageal cancer in Uruguay. *Cancer Res* 1990; **50**: 426-431

39 **De Stefani E**, Correa P, Oreggia F, Deneo-Pellegrini H, Fernandez G, Zavala D, Carzoglio J, Leiva J, Fontham E, Rivero S. Black tobacco, wine and mate in oropharyngeal cancer. A case-control study from Uruguay. *Rev Epidemiol Sante Publique* 1988; **36**: 389-394

40 **Jiang JM**, Zeng XJ, Chen JS, Li JY, Zhang KL, Wu YP, Liu BQ. Smoking and mortality from esophageal cancer in China: a large case-control study of 19,734 male esophageal cancer deaths and 104,846 living spouse controls. *Int J Cancer* 2006; **119**: 1427-1432

41 **Nasrollahzadeh D**, Kamangar F, Aghcheli K, Sotoudeh M, Islami F, Abnet CC, Shakeri R, Pourshams A, Marjani HA, Nouraie M, Khatibian M, Semnani S, Ye W, Boffetta P, Dawsey SM, Malekzadeh R. Opium, tobacco, and alcohol use in relation to oesophageal squamous cell carcinoma in a high-risk area of Iran. *Br J Cancer* 2008; **98**: 1857-1863

42 **Pandeya N**, Williams GM, Sadhegi S, Green AC, Webb PM, Whiteman DC. Associations of duration, intensity, and quantity of smoking with adenocarcinoma and squamous cell carcinoma of the esophagus. *Am J Epidemiol* 2008; **168**: 105-114

43 **Rossini AR**, Hashimoto CL, Iriya K, Zerbini C, Baba ER, Moraes-Filho JP. Dietary habits, ethanol and tobacco consumption as predictive factors in the development of esophageal carcinoma in patients with head and neck neoplasms. *Dis Esophagus* 2008; **21**: 316-321

44 **Wu M**, Zhao JK, Hu XS, Wang PH, Qin Y, Lu YC, Yang J, Liu AM, Wu DL, Zhang ZF, Frans KJ, van 't Veer P. Association of smoking, alcohol drinking and dietary factors with esophageal cancer in high- and low-risk areas of Jiangsu Province, China. *World J Gastroenterol* 2006; **12**: 1686-1693

45 **Do KA**, Johnson MM, Doherty DA, Lee JJ, Wu XF, Dong Q, Hong WK, Khuri FR, Fu KK, Spitz MR. Second primary tumors in patients with upper aerodigestive tract cancers: joint effects of smoking and alcohol (United States). *Cancer Causes Control* 2003; **14**: 131-138

46 **Hashimoto CL**, Iriya K, Baba ER, Navarro-Rodriguez T, Zerbini MC, Eisig JN, Barbuti R, Chinzon D, Moraes-Filho JP. Lugol's dye spray chromoendoscopy establishes early diagnosis of esophageal cancer in patients with primary head and neck cancer. *Am J Gastroenterol* 2005; **100**: 275-282

47 **Muto M**, Hironaka S, Nakane M, Boku N, Ohtsu A, Yoshida S. Association of multiple Lugol-voiding lesions with synchronous and metachronous esophageal squamous cell carcinoma in patients with head and neck cancer. *Gastrointest Endosc* 2002; **56**: 517-521

48 **Castellsagué X**, Muñoz N, De Stefani E, Victora CG, Castelletto R, Rolón PA. Influence of mate drinking, hot beverages and diet on esophageal cancer risk in South America. *Int J Cancer* 2000; **88**: 658-664

49 **de Barros SG**, Ghisolfi ES, Luz LP, Barlem GG, Vidal RM, Wolff FH, Magno VA, Breyer HP, Dietz J, Grüber AC, Kruel CD, Prolla JC. [High temperature "matè" infusion drinking in a population at risk for squamous cell carcinoma of the esophagus]. *Arq Gastroenterol* 2000; **37**: 25-30

50 **Rolón PA**, Castellsagué X, Benz M, Muñoz N. Hot and cold mate drinking and esophageal cancer in Paraguay. *Cancer Epidemiol Biomarkers Prev* 1995; **4**: 595-605

51 **Victora CG**, Muñoz N, Horta BL, Ramos EO. Patterns of maté drinking in a Brazilian city. *Cancer Res* 1990; **50**: 7112-7115

52 **Fagundes RB**, Abnet CC, Strickland PT, Kamangar F, Roth MJ, Taylor PR, Dawsey SM. Higher urine 1-hydroxy pyrene glucuronide (1-OHPG) is associated with tobacco smoke exposure and drinking maté in healthy subjects from Rio Grande do Sul, Brazil. *BMC Cancer* 2006; **6**: 139

53 **Kamangar F**, Schantz MM, Abnet CC, Fagundes RB, Dawsey SM. High levels of carcinogenic polycyclic aromatic hydrocarbons in mate drinks. *Cancer Epidemiol Biomarkers Prev* 2008; **17**: 1262-1268

54 **Hirota WK**, Zuckerman MJ, Adler DG, Davila RE, Egan J, Leighton JA, Qureshi WA, Rajan E, Fanelli R, Wheeler-Harbaugh J, Baron TH, Faigel DO. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. *Gastrointest Endosc* 2006; **63**: 570-580

55 **Dawsey SM**, Yu Y, Taylor PR, Li JY, Shen Q, Shu YJ, Liu SF, Zhao HZ, Cao SG, Wang GQ. Esophageal cytology and subsequent risk of esophageal cancer. A prospective follow-up study from Linxian, China. *Acta Cytol* 1994; **38**: 183-192

56 **Dawsey SM**, Shen Q, Nieberg RK, Liu SF, English SA, Cao J, Zhou B, Wang GQ, Lewin KJ, Liu FS, Roth MJ, Taylor PR. Studies of esophageal balloon cytology in Linxian, China. *Cancer Epidemiol Biomarkers Prev* 1997; **6**: 121-130

57 **Pan QJ**, Roth MJ, Guo HQ, Kochman ML, Wang GQ, Henry M, Wei WQ, Giffen CA, Lu N, Abnet CC, Hao CQ, Taylor PR, Qiao YL, Dawsey SM. Cytologic detection of esophageal squamous cell carcinoma and its precursor lesions using balloon samplers and liquid-based cytology in asymptomatic adults in Llinxian, China. *Acta Cytol* 2008; **52**: 14-23

58 **Roth MJ**, Liu SF, Dawsey SM, Zhou B, Copeland C, Wang GQ, Solomon D, Baker SG, Giffen CA, Taylor PR. Cytologic detection of esophageal squamous cell carcinoma and precursor lesions using balloon and sponge samplers in asymptomatic adults in Linxian, China. *Cancer* 1997; **80**: 2047-2059

59 **Wang LD**, Yang HH, Fan ZM, Lü XD, Wang JK, Liu XL, Sun Z, Jiang YN, He X, Zhou Q. Cytological screening and 15 years' follow-up (1986-2001) for early esophageal squamous cell carcinoma and precancerous lesions in a high-risk population in Anyang County, Henan Province, Northern China. *Cancer Detect Prev* 2005; **29**: 317-322

60 **Solomon D**, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, Raab S, Sherman M, Wilbur D, Wright T, Young N. The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA* 2002; **287**: 2114-2119

61 **Yang H**, Berner A, Mei Q, Giercksky KE, Warloe T, Yang G, Cui J, Suo Z, Zhang S, Nesland JM. Cytologic screening for esophageal cancer in a high-risk population in Anyang County, China. *Acta Cytol* 2002; **46**: 445-452

62 **Dawsey SM**, Lewin KJ, Wang GQ, Liu FS, Nieberg RK, Yu Y, Li JY, Blot WJ, Li B, Taylor PR. Squamous esophageal histology and subsequent risk of squamous cell carcinoma of the esophagus. A prospective follow-up study from Linxian, China. *Cancer* 1994; **74**: 1686-1692

63 **Lopes AB**, Reichert R, Muller LB, Moraes CM, Capra AM, Prolla JC, Diehl AR, Meurer L, Barros SG, Fagundes RB. RS Balloon cytology accuracy for identification of precursor lesions in individuals at risk for squamous cell carcinoma of the esophagus: preliminary results. *Gut* 2009; 58 [supplement II]: A288-A289.

64 **Lopes AB**, Müller LB, Reichert R, Moraes CM, Capra AM, Prolla JC, Diehl AR, Meurer L, de Barros SG, Fagundes RB. Detecting p53 immunoexpression in esophageal mucosa with exfoliative cytology in individuals at risk for squamous cell carcinoma of the esophagus. *Acta Cytol* 2010; **54**: 31-38

65 **Adams L**, Roth MJ, Abnet CC, Dawsey SP, Qiao YL, Wang GQ, Wei WQ, Lu N, Dawsey SM, Woodson K. Promoter methylation in cytology specimens as an early detection marker for esophageal squamous dysplasia and early esophageal squamous cell carcinoma. *Cancer Prev Res (Phila)* 2008; **1**: 357-361

66 **McGruder BM**, Atha DH, Wang W, Huppi K, Wei WQ, Abnet CC, Qiao YL, Dawsey SM, Taylor PR, Jakupciak JP. Real-time telomerase assay of less-invasively collected esophageal cell samples. *Cancer Lett* 2006; **244**: 91-100

67 **Grüber AC**, de Barros SG, Pütten AC, Gigante L, Coelho N, Sekine S, Prolla JC. Esophageal dysplasia and chronic esophagitis: detection at upper gastrointestinal tract endoscopy. *Arq Gastroenterol* 1998; **35**: 258-263

68 **Dawsey SM**, Fleischer DE, Wang GQ, Zhou B, Kidwell JA, Lu N, Lewin KJ, Roth MJ, Tio TL, Taylor PR. Mucosal iodine staining improves endoscopic visualization of squamous dysplasia and squamous cell carcinoma of the esophagus in Linxian, China. *Cancer* 1998; **83**: 220-231

69 **Fagundes RB**, de Barros SG, Pütten AC, Mello ES, Wagner M, Bassi LA, Bombassaro MA, Gobbi D, Souto EB. Occult dysplasia is disclosed by Lugol chromoendoscopy in alcoholics at high risk for squamous cell carcinoma of the esophagus. *Endoscopy* 1999; **31**: 281-285

70 **Freitag CP**, Barros SG, Kruel CD, Putten AC, Dietz J, Gruber AC, Diehl AS, Meurer L, Breyer HP, Wolff F, Vidal R, Arruda CA, Luz LP, Fagundes RB, Prolla JC. Esophageal dysplasias are detected by endoscopy with Lugol in patients at risk for squamous cell carcinoma in southern Brazil. *Dis Esophagus* 1999; **12**: 191-195

71 **Misumi A**, Harada K, Murakami A, Arima K, Kondo H, Akagi M, Yagi Y, Ikeda T, Baba K, Kobori Y. Role of Lugol dye endoscopy in the diagnosis of early esophageal cancer. *Endoscopy* 1990; **22**: 12-16

72 **Yokoyama A**, Ohmori T, Makuuchi H, Maruyama K, Okuyama K, Takahashi H, Yokoyama T, Yoshino K, Hayashida M, Ishii H. Successful screening for early esophageal cancer in alcoholics using endoscopy and mucosa iodine staining. *Cancer* 1995; **76**: 928-934

73 **Yokoyama A**, Muramatsu T, Ohmori T, Makuuchi H, Higuchi S, Matsushita S, Yoshino K, Maruyama K, Nakano M, Ishii H. Multiple primary esophageal and concurrent upper aerodigestive tract cancer and the aldehyde dehydrogenase-2 genotype of Japanese alcoholics. *Cancer* 1996; **77**: 1986-1990

74 **Ban S**, Toyonaga A, Harada H, Ikejiri N, Tanikawa K. Iodine staining for early endoscopic detection of esophageal cancer in alcoholics. *Endoscopy* 1998; **30**: 253-257

75 **Shimizu Y**, Tukagoshi H, Fujita M, Hosokawa M, Kato M, Asaka M. Endoscopic screening for early esophageal cancer by iodine staining in patients with other current or prior primary cancers. *Gastrointest Endosc* 2001; **53**: 1-5

76 **Bloomfeld RS**, Bridgers DI, Pineau BC. Sensitivity of upper endoscopy in diagnosing esophageal cancer. *Dysphagia* 2005; **20**: 278-282

77 **Heresbach D**, Leray E, d'Halluin PN, Cholet F, Lapalus MG, Gaudric M, Ben Soussan E, Gaudin JL, Vahedi K, Quentin V, Filoche B, Saurin JC, Chaussade S, Ponchon T. Diagnostic accuracy of esophageal capsule endoscopy versus conventional upper digestive endoscopy for suspected esophageal squamous cell carcinoma. *Endoscopy* 2010; **42**: 93-97

78 **Gono K**, Obi T, Yamaguchi M, Ohyama N, Machida H, Sano Y, Yoshida S, Hamamoto Y, Endo T. Appearance of enhanced tissue features in narrow-band endoscopic imaging. *J Biomed Opt* 2004; **9**: 568-577

79 **Yoshida T**, Inoue H, Usui S, Satodate H, Fukami N, Kudo SE. Narrow-band imaging system with magnifying endoscopy for superficial esophageal lesions. *Gastrointest Endosc* 2004; **59**: 288-295

80 **Takenaka R**, Kawahara Y, Okada H, Hori K, Inoue M, Kawano S, Tanioka D, Tsuzuki T, Uemura M, Ohara N, Tominaga S, Onoda T, Yamamoto K. Narrow-band imaging provides reliable screening for esophageal malignancy in patients with head and neck cancers. *Am J Gastroenterol*

2009; **104**: 2942-2948
81 **Lee YC**, Wang CP, Chen CC, Chiu HM, Ko JY, Lou PJ, Yang TL, Huang HY, Wu MS, Lin JT, Hsiu-Hsi Chen T, Wang HP. Transnasal endoscopy with narrow-band imaging and Lugol staining to screen patients with head and neck cancer whose condition limits oral intubation with standard endoscope (with video). *Gastrointest Endosc* 2009; **69**: 408-417
82 **Ishihara R**, Inoue T, Uedo N, Yamamoto S, Kawada N, Tsujii Y, Kanzaki H, Hanafusa M, Hanaoka N, Takeuchi Y, Higashino K, Iishi H, Tatsuta M, Tomita Y, Ishiguro S. Significance of each narrow-band imaging finding in diagnosing squamous mucosal high-grade neoplasia of the esophagus. *J Gastroenterol Hepatol* 2010; **25**: 1410-1415
83 **Lee CT**, Chang CY, Lee YC, Tai CM, Wang WL, Tseng PH, Hwang JC, Hwang TZ, Wang CC, Lin JT. Narrow-band imaging with magnifying endoscopy for the screening of esophageal cancer in patients with primary head and neck cancers. *Endoscopy* 2010; **42**: 613-619
84 **Muto M**, Minashi K, Yano T, Saito Y, Oda I, Nonaka S, Omori T, Sugiura H, Goda K, Kaise M, Inoue H, Ishikawa H, Ochiai A, Shimoda T, Watanabe H, Tajiri H, Saito D. Early detection of superficial squamous cell carcinoma in the head and neck region and esophagus by narrow band imaging: a multicenter randomized controlled trial. *J Clin Oncol* 2010; **28**: 1566-1572
85 **Ishihara R**, Takeuchi Y, Chatani R, Kidu T, Inoue T, Hanaoka N, Yamamoto S, Higashino K, Uedo N, Iishi H, Tatsuta M, Tomita Y, Ishiguro S. Prospective evaluation of narrow-band imaging endoscopy for screening of esophageal squamous mucosal high-grade neoplasia in experienced and less experienced endoscopists. *Dis Esophagus* 2010; **23**: 480-486
86 **Yoshida Y**, Goda K, Tajiri H, Urashima M, Yoshimura N, Kato T. Assessment of novel endoscopic techniques for visualizing superficial esophageal squamous cell carcinoma: autofluorescence and narrow-band imaging. *Dis Esophagus* 2009; **22**: 439-446
87 **Suzuki H**, Saito Y, Ikehara H, Oda I. Evaluation of visualization of squamous cell carcinoma of esophagus and pharynx using an autofluorescence imaging videoendoscope system. *J Gastroenterol Hepatol* 2009; **24**: 1834-1839

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CASE REPORT

Endoscopic submucosal dissection for esophageal granular cell tumor using the clutch cutter

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Abstract

Endoscopic submucosal dissection (ESD) with a knife is a technically demanding procedure associated with a high complication rate. The shortcomings of this method are the deficiencies of fixing the knife to the target lesion, and of compressing it. These shortcomings can lead to major complications such as perforation and bleeding. To reduce the risk of complications related to ESD, we developed a new grasping type scissors forceps (Clutch Cutter®, Fujifilm, Japan) which can grasp and incise the targeted tissue using an electrosurgical current. Esophagogastroduodenoscopy on a 59-year-old Japanese man revealed a 16mm esophageal submucosal nodule with central depression. Endoscopic ultrasonography demonstrated a hypoechoic solid tumor limited to the submucosa without lymph node involvement. The histologic diagnosis of the specimen obtained by biopsy was granular cell tumor. It was safely and accurately resected without unexpected incision by ESD using the CC. No delayed hemorrhage or perforation occurred. Histological examination confirmed that the granular cell tumor was completely excised with negative resection margin.We report herein a case of esophageal granular cell tumor successfully treated by an ESD technique using the CC.

Key words: Endoscopic submucosal dissection; Esophageal granular cell tumor; Clutch Cutter; Endoscopic therapy; Grasping type scissors forceps

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INTRODUCTION

Granular cell tumors (GCT) of the esophagus are rare neoplasms and their diagnosis is mainly based on histopathologic examination of endoscopic biopsies. At present, GCT treatment is not established. Until recently, management consisted of 2 relatively unsatisfactory options: observation without a definitive tissue diagnosis,

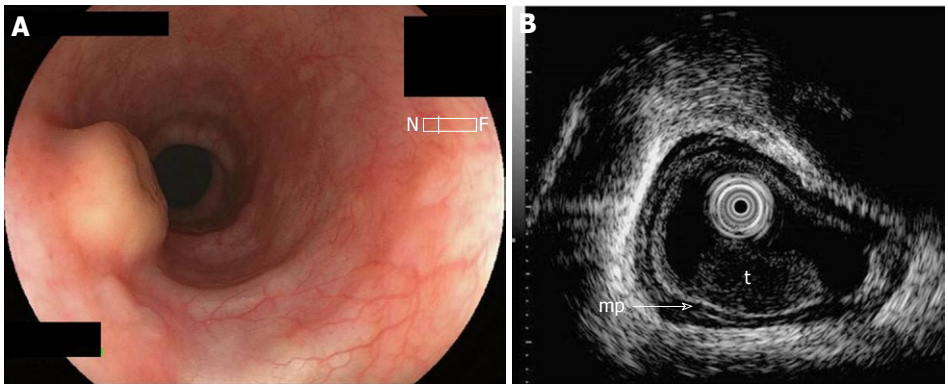

Figure 1 Pretherapeutic examinations of esophageal granular cell tumor. A: Endoscopic view of the yellowish submucosal tumor with a central depression in the middle esophagus; B: Endoscopic ultrasonography showing a hypoechoic solid tumor (t) in the submucosa; Arrow-mp: Muscularis propria.

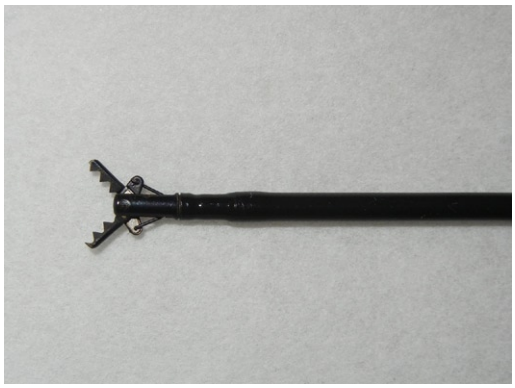

Figure 2 Distal tip of the Clutch Cutter. The outer side of the forceps is insulated so that electrosurgical current energy is concentrated at the blade to avoid burning the surrounding tissue.

and surgical resection[1]. Current advances in endoscopic techniques and technology have greatly enhanced the diagnosis and treatment of gastrointestinal malignancy. Endoscopic resection can greatly improve the management of submucosal tumors (SMT) of the gastrointestinal tract[2-6]. SMT can be resected easily and safely using this treatment method. However, endoscopic resection of SMT is sometimes inappropriate for complete resection[7]. Endoscopic submucosal dissection (ESD) has been reported to improve the rate of successful en-bloc resection in early GI tract tumors[8].Furthermore, ESD can accurately control the depth of submucosal exfoliation under endoscopic view. However, ESD, and particularly the process of submucosal dissection, is technically difficult and carries a high risk of perforation and bleeding[9-12]. Conventional devices for submucosal incision such as the IT knife and needle knife merely bring the knife in contact with the submucosal tissue and cutting is performed using an electrosurgical current. These cutting methods without fixing the knife to the target have a potential risk of incomplete resections or major complications due to unexpected incision due to pulsation or respiratory movement. To resolve the problems related to ESD using a conventional knife, we have developed the Clutch Cutter (CC), which can accurately grasp and incise the targeted tissue using an electrosurgical current[13,14]. In our previous study of early gastric neoplasms, we resected 35 tumors safely and easily without unintentional incision by ESD using the CC[15]. In this report, we first describe a new method of ESD using the CC for esophageal granular cell tumor.

CASE REPORT

Esophagogastroduodenoscopy (EGD) on a 59-year-old man revealed a 16mm esophageal submucosal nodule with a central depression (Figure1A). The histologic diagnosis of the specimen obtained by biopsy was granular cell tumor. Subsequent endoscopic ultrasonography (EUS) demonstrated a hypoechoic solid tumor in the submucosa without lymph node involvement (Figure 1B). It was treated by endoscopic submucosal dissection using a newly developed grasping type scissors forceps (Clutch Cutter®, DP2618DT; Fujifilm, Odawara, Japan) (Figure 2)[13] after obtaining written informed consent from the patient. A two channel multi-bending endoscope (GIF-2T240M; Olympus, Tokyo, Japan) was used in this case. During ESD, the patient was sedated with an intravenous injection of flunitrazepam (0.4 mg) and pethidine (35mg). The ESD technique using the CC was as follows: Marking dots were placed approximately a few millimeters outside the margin of the lesion with a hook knife (KD-620LR; Olympus, Tokyo, Japan) and a coagulation current 20W (Forced coagulation mode) created by an electrosurgical generator (ICC 200; Erbe, Tübingen, Germany). Next, a hyaluronic acid solution (MucoUp: Johnson and Johnson Co., Tokyo, Japan) mixed with a small volume of epinephrine and indigo carmine dye was injected into the submucosal layer around the target lesion to lift the entire lesion. The lesion was separated from the surrounding normal mucosa (Figure 3A) around the lesion with the CC using an electrosurgical current (Autocut mode 120W). A piece of submucosal tissue was grasped and cut with the CC (Autocut mode 120W) to achieve submucosal excision. During the submucosal dissection, ESD using the CC accurately controlled the depth of submucosal excision

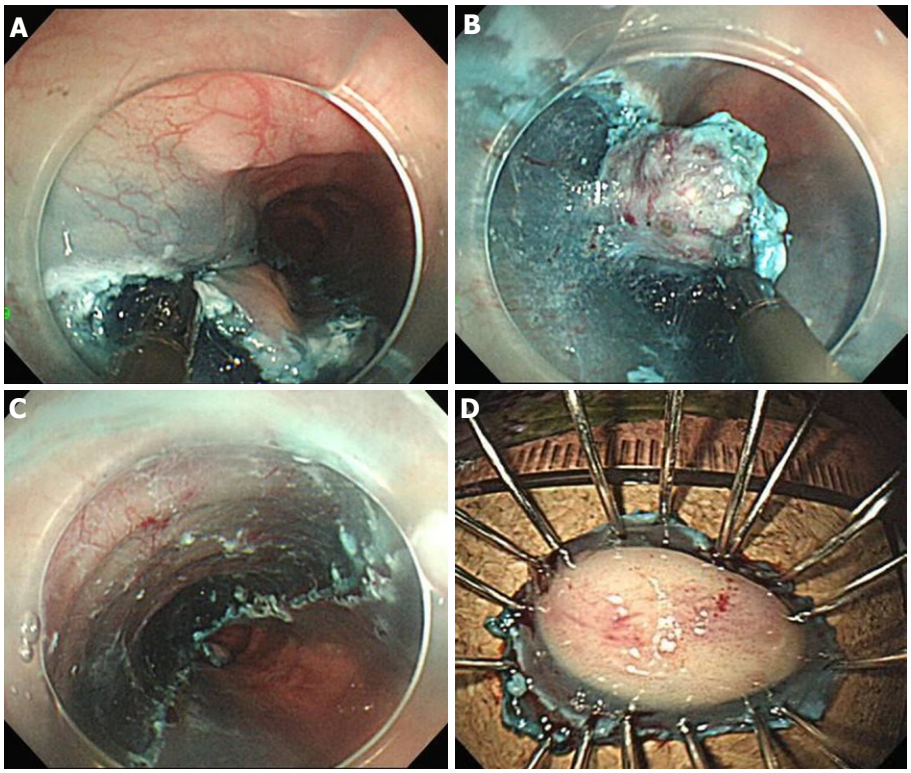

Figure 3 Endoscopic view of the procedure of endoscopic submucosal dissection using the Clutch Cutter. A: Endoscopic view of partial circumferential incision of the tumor using the Clutch Cutter (CC); B: Endoscopic view of the submucosal exfoliation under the tumor using the CC; C: The lesion is cut completely from the muscle layer; D: The resected specimen showing curative en bloc resection of the lesion.

under endoscopic vision (Figure 3B). Finally, the lesion was completely resected (en bloc resection) by CC (Figures 3C-D). ESD was completed in 59 min. Macroscopically, the mass was yellowish-white and solid, measuring 16 mm × 10 mm in diameter. Microscopically, the tumor was composed of small uniform cells, arranged in small nests and cords and with an anastomosing ribbon-like pattern in the submucosal layer. These cells had abundant granular cytoplasm and small round nuclei. Immunohistochemically, the tumor cells were positive for S-100 protein. The vertical and horizontal cut margins were negative. There was no lymphovascular invasion. These findings established curative resection of the granular cell tumor (Figure 4). After ESD, the patient remained in hospital and was prohibited from eating until the third day after ESD. Laboratory findings and chest and abdominal X-ray showed no negative changes after ESD. He was permitted oral soft food and discharged 6 d after the procedure. No hemorrhage, perforation, or other complications occurred.

Newly developed Grasping type Scissors Forceps (Clutch Cutter®)

The Clutch Cutter® (DP2618DT, Fujifilm Corporation, Odawara, Japan) (Figure 2) can grasp and cut a piece of tissue with an electrosurgical current. It has a 0.4 mm wide and 3 mm long serrated cutting edge to facilitate grasping the tissue. The outer side of the forceps is insulated so that electrosurgical current energy is concentrated at the blade to avoid burning the surrounding tissue. Furthermore, the forceps can be rotated to the desired orientation. The diameter of the forceps is 2.7 mm. The CC is available for standard endoscopes with a working channel width of 2.8 mm or more. This device, which is disposable and not reusable, was used for marking, circumferential marginal incision, submucosal dissection and hemostatic treatment.

Ethical considerations

The advantages and disadvantages of ESD using the CC, as well as alternative endoscopic options (ESD using conventional device, endoscopic mucosal resection, *etc*), were discussed with the patient. The patient was aware of the experimental nature of the planned treatment. He gave his written informed consent for the designated intervention. This study was reviewed and approved by the ethics committee of Aso Iizuka Hospital. It was conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with good clinical practice.

DISCUSSION

Esophageal GCT account for one-third of gastrointestinal tract GCT. Esophageal GCT are generally considered benign, although a few malignant GCT have been reported[16,17]. Six histologic criteria were assessed: necrosis, spindling, vesicular nuclei with large nucleoli, increased mitotic activity (> 2 mitoses/10 high power fields at 200× magnification), high nuclear to cytoplasmic (N:C) ratio, and pleomorphism[18]. Neoplasms that met three or more of these criteria were classified as histologically malignant; those that met one or two criteria were classified as atypical; and those that displayed only focal pleomorphism but fulfilled none of the other criteria were classified as benign. Ordinary endoscopic biopsy

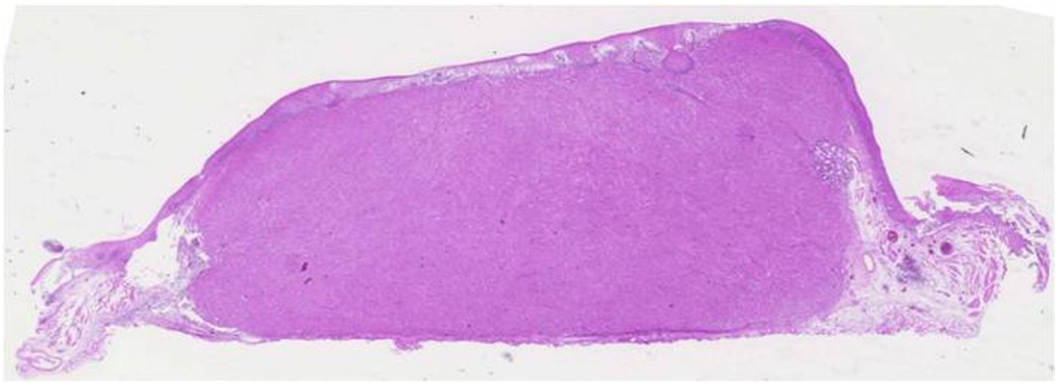

Figure 4 Microscopic appearance of the tumor. The resected tumor is covered with normal mucosa (hematoxylin and eosin; original magnification, x 2).

involving a small amount of tissue is unlikely to yield diagnostic tissue because the tumor typically is covered by normal mucosa. Therefore, preoperative diagnosis is difficult without total resection of the tumor. When we make a diagnosis of GCT endoscopically, we should consider the possibility of malignancy.

For this reason, endoscopic resection is currently considered an appropriate approach for total resection of GCT[2-4,19]. However,various modified endoscopic therapies, such as endoscopic mucosal resection (EMR)[2], endoscopic aspiration lumpectomy (EAL)[5], strip biopsy[6], endoscopic mucosal resection using a ligating device (EMRL)[4] and EUS-guided endoscopic resection using band ligation[19] have been reported. Submucosal tumors smaller than 1 cm in diameter and separate from the muscularis propria can be resected by endoscopic therapy. However, endoscopic resection of submucosal tumor is sometimes inappropriate for complete resection[7]. Use of conventional methods is often associated with marginal involvement by residual tumor requiring subsequent intervention.

In such circumstances, ESD should be applied[20]. ESD was originally developed to obtain one-piece resection for early gastric cancers[10-14]. ESD has the advantage of permitting en bloc resection and histologically complete resection. On the other hand, this method has the disadvantages of a long procedure time and a high frequency of complications, as well as demanding a high level of technical skill. However, ESD can control the depth of submucosal dissection under endoscopic view[9-14]. Therefore, ESD is a theoretically suitable therapeutic option for GCT located within the submucosa[21]. If the tumor invades the muscularis propria, ESD is a contraindication due to the risk of perforation and metastasis. Pretherapeutic EUS is vital for decision making concerning the indication of ESD for this disease.

Endoscopic removal with ESD of a granular cell tumor of the esophagus was first described by Aoki *et al*[22] in 2005. Since this first report, there have been at least 2 documented reports of esophageal GCT successfully removed with ESD. In these three cases, a knife device was used for ESD[21-23]. Incision using knife devices merely brings the knife in contact with the tissue and cut using electrosurgical current. These cutting processes without fixing the device to the targeted tissue make it difficult to place the knife accurately during electrosurgical incision because of cardiac beat, respiratory movement, and peristalsis. Lack of complete endoscopy control can cause unwanted incision and may result in incomplete resection or severe complications such as perforation and bleeding[9-12].

Our approach was to perform endoscopic resection with a CC which can be passed through the ordinary working channel. This device was developed by us for ESD of early gastric cancer[13,14]. It has a thin serrated cutting edge to facilitate grasping the tissue. The outer side of the forceps is insulated so that electrosurgical current energy is concentrated at the blade to avoid burning the surrounding tissue. Furthermore, the forceps can be rotated to the desired orientation. Theoretically, the main advantage of the CC for ESD is the fixed device, which can accurately control the depth of submucosal exfoliation with good endoscopic vision[14]. The CC can be used to grasp the targeted tissue again if necessary, before electrosurgical cutting. The maximal advantage of the CC is having the visual confirmation step for accurate and safe targeting by the device before cutting during the grasping stage. Furthermore, the CC can reduce post-cut hemorrhage by a compression effect similar to a polypectomy snare[14]. Thus,the grasping step before cutting allows accurate targeting and compression of the vessel, and reduces the chance of incomplete resection (positive vertical margin) and major complications (perforation and bleeding). In this case, it was safe and accurate to resect the esophageal GCT with sufficient negative resection margin using the CC. We believe this technique has the potential to become the method of choice for removal of GI tract GCT when the tumor is limited to the submucosa.

REFERENCES

1 **Waxman I**, Saitoh Y, Raju GS, Watari J, Yokota K, Reeves AL, Kohgo Y. High-frequency probe EUS-assisted endoscopic mucosal resection: a therapeutic strategy for submucosal tumors of the GI tract. *Gastrointest Endosc* 2002; **55**: 44-49

2 **Yasuda I**, Tomita E, Nagura K, Nishigaki Y, Yamada O,

Kachi H. Endoscopic removal of granular cell tumors. *Gastrointest Endosc* 1995; **41**: 163-167
3 **Esaki M**, Aoyagi K, Hizawa K, Nakamura S, Hirakawa K, Koga H, Yao T, Fujishima M. Multiple granular cell tumors of the esophagus removed endoscopically: a case report. *Gastrointest Endosc* 1998; **48**: 536-539
4 **Shikuwa S**, Matsunaga K, Osabe M, Ofukuji M, Omagari K, Mizuta Y, Takeshima F, Murase K, Otani H, Ito M, Shimokawa I, Fujii M, Kohno S. Esophageal granular cell tumor treated by endoscopic mucosal resection using a ligating device. *Gastrointest Endosc* 1998; **47**: 529-532
5 **Yazumi S**, Takahashi R, Kajiyama T, NakaseH, WatanabeN, OhanaM, MatsumotoS, SenoH, SawadaM, UchidaK, NabeshimaM, OkazakiK, ChibaT.Comparison of histological analysis and endosonographic features in esophageal granular cell tumors. *Digestive Endoscopy* 2003; **15**: 284-288
6 **Urabe M**, Daibo M, Gonda H, Sakakibara N. Three cases of esophageal granular cell tumor. *Digestive Endoscopy* 1996; **8**: 32-37
7 **Wehrmann T**, Martchenko K, Nakamura M, Riphaus A, Stergiou N. Endoscopic resection of submucosal esophageal tumors: a prospective case series. *Endoscopy* 2004; **36**: 802-807
8 **Hirao M**, Masuda K, Asanuma T, Naka H, Noda K, Matsuura K, Yamaguchi O, Ueda N. Endoscopic resection of early gastric cancer and other tumors with local injection of hypertonic saline-epinephrine. *Gastrointest Endosc* ; **34**: 264-269
9 **Onozato Y**, Kakizaki S, Ishihara H, Iizuka H, Sohara N, Okamura S, Mori M, Itoh H. Endoscopic submucosal dissection for rectal tumors. *Endoscopy* 2007; **39**: 423-427
10 **Ono H**, Kondo H, Gotoda T, Shirao 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
11 **Fujishiro M**. Endoscopic submucosal dissection for stomach neoplasms. *World J Gastroenterol* 2006; **12**: 5108-5112
12 **Neuhaus H**, Costamagna G, Devière J, Fockens P, Ponchon T, Rösch T. Endoscopic submucosal dissection (ESD) of early neoplastic gastric lesions using a new double-channel endoscope (the "R-scope"). *Endoscopy* 2006; **38**: 1016-1023
13 **Akahoshi K**, Akahane H, Murata A, Akiba H, Oya M. Endoscopic submucosal dissection using a novel grasping type scissors forceps. *Endoscopy* 2007; **39**: 1103-1105
14 **Akahoshi K**, Honda K, Akahane H, Akiba H, Matsui N, Motomura Y, Kubokawa M, Endo S, Higuchi N, Oya M. Endoscopic submucosal dissection by using a grasping-type scissors forceps: a preliminary clinical study (with video). *Gastrointest Endosc* 2008; **67**: 1128-1133
15 **Akahoshi K**, Honda K, Motomura Y, Kubokawa M, Okamoto R, Osoegawa T, Nakama N, Kashiwabara Y, Higuchi N, Tanaka Y, Oya M, Nakamura K. Endoscopic submucosal dissection using a grasping-type scissors forceps for early gastric cancers and adenomas. *Dig Endosc* 2011; **23**: 24-29
16 **Orlowska J**, Pachlewski J, Gugulski A, Butruk E. A conservative approach to granular cell tumors of the esophagus: four case reports and literature review. *Am J Gastroenterol* 1993; **88**: 311-315
17 **Vuyk HD**, Snow GB, Tiwari RM, van Velzen D, Veldhuizen RW. Granular cell tumor of the proximal esophagus. A rare disease. *Cancer* 1985; **55**: 445-449
18 **Fanburg-Smith JC**, Meis-Kindblom JM, Fante R, Kindblom LG. Malignant granular cell tumor of soft tissue: diagnostic criteria and clinicopathologic correlation. *Am J Surg Pathol* 1998; **22**: 779-794
19 **Saito H**, Akahoshi K, Oya M, Kubokawa M, Akiho H, Sumida Y, Fujimaru T, Higuchi N, Matsumoto M. EUS-guided endoscopic resection using band ligation of oesophageal granular cell tumour: report of a case. *Acta Gastroenterol Belg 1998*; **68**: 272-275
20 **Fujishiro M**. Perspective on the practical indications of endoscopic submucosal dissection of gastrointestinal neoplasms. *World J Gastroenterol* 2008; **14**: 4289-4295
21 **Hülagü S**, Sentürk O, Aygün C, Gürbüz Y, Kocaman O, Celebi A, Konduk T. Granular cell tumor of esophagus removed with endoscopic submucosal dissection. *Turk J Gastroenterol* 2007; **18**: 188-191
22 **Aoki H**, Onohara Y, Iizuka H, Sagawa T, Arai H, Takayama H, Abe T, Tomizawa N, Ogawa T, Ishihara H, Motegi A, Ito H. A case of esophageal granular cell tumor successfully resected by endoscopic submucosal dissection(ESD). *Progress of Digestive Endoscopy* 2005 ; **67**: 2: 54-55
23 **Okamoto Y**, Sasaki Y, Yagihashi N, Yamai K, Sato K, Chiba H, Tinda D, Saito M, Suzuki H, Hachimori H, Kawabe H, Fukuda S. An esophageal granularcell tumor successfully removed with endoscopic submucosal dissection. *Gastroenterol Endosc* 2010; **52**: 1857-1865

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Events Calendar 2012

January 19-21, 2012
American Society of Clinical Oncology 2012 Gastrointestinal Cancers Symposium
San Francisco, CA 3000, United States

January 19-21, 2012
2012 Gastrointestinal Cancers Symposium
San Francisco, CA 94103, United States

January 20-21, 2012
American Gastroenterological Association Clinical Congress of Gastroenterology and Hepatology
Miami Beach, FL 33141, United States

February 2-4, 2012
14th Dusseldorf International Endoscopy Symposium 2012
Dusseldorf, Germany

February 24-27, 2012
Canadian Digestive Diseases Week 2012
Montreal, Canada

March 1-3, 2012
International Conference on Nutrition and Growth 2012
Paris, France

March 7-10, 2012
Society of American Gastrointestinal and Endoscopic Surgeons Annual Meeting
San Diego, CA 92121, United States

March 12-14, 2012
World Congress on Gastroenterology and Urology
Omaha, NE 68197, United States

March 30-April 2, 2012
Mayo Clinic Gastroenterology and Hepatology
San Antonio, TX 78249, United States

March 31-April 1, 2012
5th Annual Endoscopy Directors Meeting Endoscopy Unit Management in the 21st Century: Issues, Solutions, and Plans for the Future
Washington, DC 20057, United States

April 8-10, 2012
9th International Symposium on Functional GI Disorders
Milwaukee, WI 53202, United States

April 15-17, 2012
European Multidisciplinary Colorectal Cancer Congress 2012
Prague, Czech

April 19-21, 2012
Internal Medicine 2012
New Orleans, LA 70166, United States

April 20-22, 2012
Diffuse Small Bowel and Liver Diseases
Melbourne, Australia

April 22-24, 2012
EUROSON 2012 EFSUMB Annual Meeting
Madrid, Spain

April 28, 2012
Issues in Pediatric Oncology
Kiev, Ukraine

May 3-5, 2012
9th Congress of The Jordanian Society of Gastroenterology
Amman, Jordan

May 7-10, 2012
Digestive Diseases Week
Chicago, IL 60601, United States

May 17-21, 2012
2012 ASCRS Annual Meeting-American Society of Colon and Rectal Surgeons
Hollywood, FL 1300, United States

May 18-23, 2012
SGNA: Society of Gastroenterology Nurses and Associates Annual Course
Phoenix, AZ 85001, United States

May 19-22, 2012
2012-Digestive Disease Week
San Diego, CA 92121, United States

June 18-21, 2012
Pancreatic Cancer: Progress and Challenges
Lake Tahoe, NV 89101, United States

September 8-9, 2012
New Advances in Inflammatory Bowel Disease
La Jolla, CA 92093, United States

September 8-9, 2012
Florida Gastroenterologic Society 2012 Annual Meeting
Boca Raton, FL 33498, United States

September 15-16, 2012
Current Problems of Gastroenterology and Abdominal Surgery
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Dnepropetrovsk, Ukraine

December 1-4, 2012
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GENERAL INFORMATION

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In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hyperten sion, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

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No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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