Short-Term Healing Process of Artificial Ulcers after Gastric Endoscopic Submucosal Dissection

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Background/Aims: The relationship between the appearance of an ulcer and postoperative bleeding after gastric endoscopic submucosal dissection (ESD) is not well understood. To explore this potential relationship, we retrospectively analyzed the short-term healing process of ESD. **Methods:** A total of 520 consecutive lesions in 434 patients seen between January 2004 and December 2009 were retrospectively investigated. At the second-look endoscopy, which occurred between 1 and 8 days after ESD, artificial ulcers were categorized into 6 patterns according to Forrest's classification: spurting bleeding, oozing bleeding, non-bleeding visible vessel, adherent clot, black base/spot, and clean base. From these data, a short-term healing model of the artificial ulcer was generated. **Results:** Ulcer base changed gradually from a bloody to a clean one. The bleeding or non-bleeding visible vessel categories, which occurred in approximately one quarter of the ulcers within 3 days of ESD, were rarely observed 4 days after ESD. **Conclusions:** Ulcers that occur after gastric ESD heal in line with a specific time course, and it appears that most healing occurs without massive bleeding. (**Gut Liver 2011;5:293-297**)

Key Words: Endoscopic submucosal dissection; Artificial ulcer; Healing process; Gastric neoplasm; Postoperative bleeding

INTRODUCTION

Endoscopic submucosal dissection (ESD) has been established as an alternative method to open surgery for a node-negative early gastric cancer, especially in Japan.¹⁻³ It is characterized by circumferential mucosal incision and submucosal dissection,

which enables *en bloc* resection even for large or ulcerative lesions.

One of major complications is postoperative bleeding, which generally occurred in approximately 5% of the patients.⁴⁻⁶ Various countermeasures are empirically taken in order to prevent it, e.g., the use of proton pump inhibitor (PPI) around ESD, postendoscopic coagulation for visible vessels on a mucosal defect immediately after the resection of a lesion, a second-look endoscopy after ESD. PPI is thought to be effective from several studies including prospective randomized trials,^{7,8} and its usefulness is generally gained acceptance in most hospitals, although there is still room for discussion about the suitable dose or duration. Postendoscopic coagulation immediately after the resection of the lesion also seems to be practiced in most hospitals and one retrospective analysis advocates the efficacy in post-ESD bleeding.⁵ The usefulness of a second-look endoscopy, however, is controversial because few analyses exist.⁶ Referring to bleeding peptic ulcers, it is generally thought that a second-look endoscopy performed a few days after stopping initial bleeding may be useful especially for high-risk patients of rebleeding.⁹⁻¹² But, the thought that it was equally useful for an artificial ulcer as well as for a bleeding peptic ulcer may be not always applicable, because the information about the artificial ulcer is too little to evaluate its efficacy satisfactory. We, therefore, retrospectively investigated the time-sequence changes of it checked by the second-look endoscopy after ESD.

MATERIALS AND METHODS

Of 551 lesions in 457 patients treated by ESD after obtaining written informed consent in our hospital from January 2004 to December 2009 (the period in which ESD technique has been

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regarded as established at our hospital), consecutive 520 lesions in 434 patients were retrospectively investigated. Excluded were 10 lesions in which perforation occurred after change of PPI due to the patient's condition, 14 lesions without second-look endoscopy, and 7 lesions with bleeding that occurred within 24 hours after ESD because those lesions less contributed to the elucidation of the natural course of artificial ulcers.

The indication of ESD were determined according to the endoscopic findings including chromoendoscopy with indigo carmine and biopsy, referring to the criteria of possible node-negative early gastric cancer by Gotoda *et al.*¹³ as followed: 1) intramucosal intestinal-type cancer without ulcerative findings, regardless in size; 2) intramucosal intestinal-type cancer with ulcerative findings, 3 cm or less in size; 3) slight invasive intestinal-type cancer into submucosa less than 500 μ m from muscularis mucosa, 3 cm or less in size; and 4) intramucosal diffuse-type cancer without ulcer findings, 2 cm or less in size. In addition, 5) adenoma difficult to distinguish from cancer or 6) technically resectable cancer endoscopically out of the above criteria for which the patients strongly desired to be resected were indicated for ESD. Clinicopathological features of the eligible lesions are shown in Table 1.

ESD techniques were precisely described elsewhere.¹⁻³ In brief, a flex-knife (KD-630L; Olympus, Tokyo, Japan) was used as the main electrosurgical knife for mucosal cutting of surrounding non-neoplastic mucosa and for submucosal dissection beneath

the lesion.² A mixture of 10% glycerin plus 5% fructose and 0.9% saline preparation (Glyceol; Chugai Pharmaceutical Co., Tokyo, Japan) or hyaluronic acid was injected into submucosa under the lesion to make submucosal fluid cushion.^{14,15} Hemostatic forceps (HDB2422W; Pentax, Tokyo, Japan) or hemostatic clips (HX-610-135 or HX-610-090L; Olympus) were used to stop bleeding or to cauterize visible vessels on the mucosal defect. If the patient's symptoms, laboratory findings, and chest and abdominal X-rays were unremarkable at the next day of ESD, a light meal was permitted and the patients were discharged within one week. From the day before ESD to at least 2 weeks after ESD, 10 mg of rabeprazole, 20 mg of omeprazole, or 30 mg of lansoprazole once daily was administered orally. Occasionally, 20 mg of intravenous omeprazole twice daily was administered during the fasting period including the day of ESD, according to the decision of doctors in charge.

A second-look endoscopy was performed to check bleeding or non-bleeding visible vessel on the artificial ulcer once between the day and 8 days after ESD. The day of second-look endoscopy was irregularly decided taking into account the day of the week when ESD was performed and the operator's convenience. If bleeding occurred or non-bleeding visible vessel was detected, (prophylactic) thermocoagulation with hemostatic forceps or mechanical hemostasis with hemostatic clips was executed. The way of hemostasis was flexibly selected according to the condition of bleeding. The treatment of (prophylactic) hemostasis was continued until active bleeding was stopped for several seconds even after flushing water or visible vessels apparently disappeared.

In case of tightly adherent clot, presence of an apparent visible vessel beneath the clot was checked by removing it. If complications occurred, the schedules were changed according to the individual patient's conditions. The patient was seen as an outpatient 2 weeks after discharge, and was checked by a follow-up endoscopy 2 months after ESD. Postoperative bleeding was defined as bleeding or non-bleeding visible vessel with massively accumulated blood in the stomach on emergency endoscopy performed due to hematemesis or melena, or progression of anemia with vital changes.

We investigated the artificial ulcers on the second-look endoscopy and categorized these ulcers into 6 patterns according to Forrest's classification.^{16,17} These ulcers were allocated into; spurting bleeding, oozing bleeding, non-bleeding visible vessel, adherent clot, black base/spot, and clean base. The ulcers which caused postoperative bleeding confirmed by emergency endoscopy were allocated into spurting bleeding, regardless of active bleeding during endoscopy. Based on the allocation, the proportion of those patterns on each postoperative day was investigated to elucidate the natural healing process on the artificial ulcer's surface. Subsequently, the bleeding rates after the second-look endoscopy according to these patterns of the ulcer were investigated.

Table 1. Characteristics of the Enrolled Cases

Characteristic	No. (Total 520 lesions)
Patient-related	
Age, mean $\pm$ SD, yr	68.5 $\pm$ 9.1
Sex, M:F	396:124
Comorbidities (present:absent)	
Hypertension	116:404
Diabetes mellitus	49:471
Heart disease	44:476
Chronic renal failure	8:512
Liver cirrhosis	20:500
Anticoagulants/platelets (used:not used)	66:454
Lesion-related	
Location (U or R:M:L)	118:182:220
Circumference (AW:GC:LC:PW)	97:90:196:137
Gross type (I/IIa:IIb/IIc:combined)	193:292:35
Ulcerative findings (present:absent)	57:463
Tumor size, mean $\pm$ SD, mm	19.0 $\pm$ 13.9
Tumor depth (mucosa:submucosa)	428:92
Histological type (carcinoma:adenoma)	447:73

SD, standard deviation; U, upper third; R, remnant stomach; M, middle third; L, lower third; AW, anterior wall; GC, greater curve; LC, lesser curve; PW, posterior wall.

Table 2. Patterns of Artificial Ulcers after Endoscopic Submucosal Dissection according to Postoperative Day

	Postoperative day							
	1	2	3	4	5	6	7	8
Spurting bleeding*	5 (2.7)	1 (3.7)	3 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Oozing bleeding	15 (8.2)	0 (0.0)	4 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-bleeding visible vessel	24 (13.1)	1 (3.7)	5 (9.3)	0 (0.0)	0 (0.0)	2 (2.0)	1 (1.3)	0 (0.0)
Adherent clot	45 (24.6)	6 (22.2)	4 (7.4)	0 (0.0)	2 (14.3)	5 (5.0)	6 (7.5)	0 (0.0)
Black base/spot	69 (37.2)	15 (55.6)	21 (38.9)	18 (72.0)	5 (35.7)	51 (51.0)	35 (43.8)	8 (21.6)
Clean base	25 (14.2)	4 (14.8)	17 (31.5)	7 (28.0)	7 (50.0)	42 (42.0)	37 (46.3)	29 (78.4)
Total	183 (100)	27 (100)	54 (100)	25 (100)	14 (100)	100 (100)	80 (100)	37 (100)

Data are presented as number (%).

*These numbers contained the emergency endoscopy performed due to postoperative bleeding.

Fig. 1. Proportion of the 6 artificial ulcer patterns according to postoperative day. Over time, the number of ulcers with a bloody appearance decreases, and a greater number are observed to have a clean base.

Statistical analysis was performed by chi-square test for categorical variables and p-value of less than 5% was considered significant. JMP version 8.0 software (SAS Institute, Cary, NC, USA) was used for all analyses.

RESULTS

The patterns of the artificial ulcer after ESD related to the postoperative day were showed in Table 2. The second-look endoscopy was performed most on the postoperative day 1 (183 lesions), and secondly on the postoperative day 6 (100 lesions). The numbers of the second-look endoscopies contained the emergency endoscopy performed due to possible postoperative bleeding.

The proportion of the patterns on each postoperative day was showed in Fig. 1. As a natural course, the ulcer seemed to change gradually from bloody to clean base. Active bleeding or non-bleeding visible vessel, which was intended for endoscopic

Table 3. Bleeding Rate after the Second-Look Endoscopy for Each Artificial Ulcer Pattern

Bleeding after the second-look endoscopy	No. (12/520)	%	95% CI
The appearance of the artificial ulcer			
Spurting bleeding*	0/10	0.0	0-27.8
Oozing bleeding*	0/19	0.0	0-16.8
Non-bleeding visible vessel*	1/33	3.0	0.5-15.3
Adherent clot [†]	0/68	0.0	0-5.4
Black base/spot [†]	8/222	3.6	1.8-7.0
Clean base [†]	3/168	1.8	0.6-5.1

CI, confidence interval.

*Endoscopic intervention was performed; [†]Endoscopic intervention was principally not performed.

hemostatic treatment, appeared on approximately a quarter of the ulcers within 3 days after ESD, but were rarely observed 4 days after ESD or later.

Bleeding after the second-look endoscopy occurred in 12 lesions. The relationship between the findings on the second-look endoscopy and bleeding after that showed in Table 3. There was no apparent tendency for bleeding after the second-look endoscopy among the patterns of the ulcers.

DISCUSSION

In the present analysis, we demonstrated the model of short-term healing process on the artificial ulcer after gastric ESD, owing to perform the second-look endoscopy once after ESD without any strict criteria. The previous studies have demonstrated that the artificial ulcer usually heals within 2 months from active stage to scarring stage,¹⁸ but this is the first report about the information of it during short interval of active stage. As Fig. 1 showed, the ulcer gradually changed from bloody appearance to clean surface covered with mucoid cap. The reason why the proportion of bloody patterns has made a dip on post-

operative day 4 is thought that the number of the second-look endoscopy performed on that day has been fewer compared to the other days. Fig. 1 implies that the second-look endoscopy should be performed relatively soon after ESD (if it was expected to be worth to be done). Although the second-look endoscopy late after ESD (and almost before discharge) may be reasonable to check the possible bleeding spot, more effective timing of it is thought to be within 3 days after ESD, because the second-look endoscopy soon after ESD can frequently meet the targets for endoscopic intervention, whereas those rarely exist on it late after ESD.

From the other side of view, Fig. 1 reflects the natural healing process of a single artificial ulcer. If clinically apparent postoperative bleeding such as spurting bleeding does not occur, the ulcer can be expected to heal without massive bleeding to some extent, even though oozing bleeding has occurred or non-bleeding visible vessel exists. That is, the figure implies that oozing bleeding may stop spontaneously, or non-bleeding visible vessel may disappear. For example, we can imagine that 217 lesions checked on the postoperative day from 6 to 8 have almost improved spontaneously without clinically-problematic bleeding, in spite of the possibility that approximately a quarter of those may have had oozing bleeding or non-bleeding visible vessel. Hemostasis for oozing bleeding or prophylactic hemostasis for non-bleeding visible vessel may be certainly effective against further bleeding, but it may merely provide subclinical benefit. Many previous studies about bleeding peptic ulcer suggest that active bleeding and non-bleeding visible vessel should be indicated for endoscopic intervention because these have high potential of rebleeding,^{9-12,17} and that is why we empirically performed the second-look endoscopy after ESD. But, the suitable treatment to a bleeding peptic ulcer cannot be applicable to the artificial ulcer because both ulcers are quite different in many features, e.g., the cause of genesis, the circumstance in the stomach, and the depth. In that point, we need to construct another new strategy of caring for the artificial ulcer, and it will become relatively looser than that for a peptic ulcer.

There is still room for discussion about the clinical efficacy of the second-look endoscopy. Fig. 1 speculates that almost all the artificial ulcers after ESD heal without massive bleeding. But, we cannot discuss about the necessity of the second-look endoscopy after ESD only from this retrospective study. Another method to explain necessity of second-look endoscopy after ESD will be needed. A prospective study with more delicate groups, fixed time of second-look endoscopy, and patient's clinical details is desired.

On the other side, advanced endoscopic tool and new therapeutic strategy for hemostasis may be invented in the future, which will help to prevent postoperative bleeding after ESD more effectively. These advancements may also decrease necessity of second-look endoscopy.

The limitation is that this study is formed by a single-cen-

tered, retrospective analysis, although this is consecutive data. Besides, the change of the appearance on the artificial ulcer which we have showed is not an accumulation of data from longitudinal observation of a single ulcer, but from each one finding of many, various ulcers. In that point, the healing process in Fig. 1 is still an assumption. Longitudinal observations of the single ulcer are ideal, but it would be impossible either clinically or ethically.

In conclusion, we could suggest the model of the short-term healing process on the artificial ulcer after gastric ESD from the findings of the second-look endoscopy. The ulcer changes from bloody to clean surface in line, and most of the ulcers are expected to heal without massive bleeding.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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