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ORIGINAL ARTICLE

Delayed bleeding and hemorrhage of mucosal defects after gastric endoscopic submucosal dissection on second-look endoscopy

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Abstract

Background Although second-look endoscopy is performed within several days after gastric endoscopic submucosal dissection (ESD), there has been no evidence supporting the usefulness of the intervention. We investigated the relationship between delayed bleeding and hemorrhage of mucosal defects after ESD on second-look endoscopy and analyzed risk factors of active bleeding on second-look endoscopy.

Methods A total of 441 consecutive ESD cases with gastric cancer or adenoma were retrospectively analyzed. Second-look endoscopy was performed in the morning after the day of ESD. Bleeding of mucosal defects on second-look endoscopy was classified according to the Forrest classification, and active bleeding was defined as Forrest Ia or Ib. Delayed bleeding was defined as hematemesis or melena after second-look endoscopy.

Results A total of 406 second-look endoscopies were performed, and delayed bleeding occurred in 11 patients. The incidence rate of delayed bleeding after second-look endoscopy in patients with Forrest Ia or Ib was significantly higher than that in patients with Forrest IIa, IIb or III (7.69 vs. 2.02 %, $p < 0.05$). Complication of a histological ulcer, large size of the resected specimen and long ESD procedure time were shown to be risk factors for hemorrhage of mucosal defects after ESD on second-look endoscopy by univariate analysis. Multivariate analysis indicated that only large size of the resected specimen was a risk factor. In a specimen size of >35 mm, the odds ratio of active bleeding on second-look endoscopy was 1.9.

Conclusion Active bleeding of mucosal defects on second-look endoscopy is a risk factor for delayed bleeding.

Keywords Endoscopic gastrointestinal surgery · Gastric cancer · Postoperative hemorrhage

Introduction

Endoscopic submucosal dissection (ESD) is now widely accepted as a standard endoscopic treatment for gastric neoplasms having a negligible risk of lymph node metastasis because of its safety and high rate of curability [1, 2]. However, the procedure can cause the formation of large iatrogenic ulcers, and it has been reported that delayed bleeding, which is a major complication of endoscopic surgery, occurs more frequently after ESD than after conventional endoscopic mucosal resection (EMR) [3]. Delayed bleeding after ESD occurs in about 5 % of patients, and endoscopic hemostasis during emergency endoscopy is effective for stopping the bleeding in most cases [4, 5].

There is no evidence supporting the usefulness of second-look endoscopy; however, second-look endoscopy after gastric ESD has been routinely performed in our hospital. We therefore retrospectively reviewed our gastric ESD cases to examine the relationship between delayed bleeding and hemorrhage of mucosal defects after ESD on second-look endoscopy, and the risk factors of active bleeding on second-look endoscopy were analyzed.

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Patients and methods

All patients provided written informed consent before treatment, and permission to study patient records was given by the Hokkaido University Hospital Review Board.

Patients

Between January 2004 and December 2012, 394 patients (301 males and 93 females, mean age 70.8 years) were admitted to our institution and received gastric ESD for gastric cancer or adenoma. A total of 441 consecutive ESDs in those patients were analyzed in this study.

Indication for ESD and ESD procedures

Our indication criteria for gastric ESD are in accordance with the Gastric Cancer Treatment Guidelines issued by the Japanese Gastric Cancer Association, and there is no size restriction for adenomas [6, 7].

Generally, standard ESD was performed using an insulation-tipped (IT) knife or an IT knife 2 (KD-610L/KD-611L, Olympus Medical Systems Co., Ltd., Tokyo, Japan), and an ICC-200 (Intelligent Cut and Coagulation; ERBE, Germany) was used as the electrosurgical unit [6, 7]. During the operation, hemostasis was carefully performed using hemostatic forceps and endoscopic hemoclippings. After removing the lesions, the iatrogenic ulcer was not endoscopically sutured, non-bleeding visible vessels and oozing were treated, and then complete hemostasis was confirmed.

During the study period, a total of 15 endoscopists including 12 trainees performed ESD. When the trainees performed ESD, supervisors gave them precise advice any time and supervised them until completion of the procedures.

Postoperative pathway

Patients with clinically evident bleeding after ESD underwent urgent endoscopy.

Second-look endoscopy was principally performed the next morning in patients without perforation and bleeding before the procedure. After we checked retention of blood or cogula in the stomach, iatrogenic ulcers were observed carefully. When active bleeding or non-bleeding visible vessels were seen after washing adherent clots, endoscopic hemostasis was performed during the procedure. Although the method for endoscopic hemostasis was decided by each endoscopist, clipping or thermocoagulation using forceps was performed for bleeding vessels and non-bleeding visible vessels. Argon plasma coagulation was used for oozing from small visible vessels and the circumference border around the iatrogenic ulcer. Third-look endoscopy before discharge was performed on postoperative day (POD) 7.

Generally, patients were allowed to drink water on POD 1 and to eat a light meal on POD 2, and they were discharged on POD 8. When perforation or post-ESD bleeding occurred, the schedules including meals and discharge were changed according to the patient's condition and operator's decision.

Principally, patients receiving antithrombotic agents including anticoagulants and/or antiplatelet drugs stopped taking them for 5–7 days before and after ESD. A heparin bridging therapy was indicated for patients with a high thromboembolic risk according to the instructions by the prescription doctors. Intravenous heparin was administered until 6 h before the procedure and was restarted soon after ESD. For all patients undergoing dialysis, the anticoagulant agent was changed to nafamostat mesylate.

Twenty mg omeprazole was administered intravenously twice a day on the day of ESD and on POD 1, and 20 mg omeprazole was administered once daily from POD 2 to 1 month after the operation [7]. Follow-up endoscopy was performed 1 month after ESD, and patients were also asked to contact us in case of hematemesis or melena after discharge.

Helicobacter pylori (*H. pylori*) infection status

Helicobacter pylori current infection status was determined when the results of at least one of the following were positive: rapid urease test (Helicocheck kit, Otsuka Pharmaceutical Co., Tokyo, Japan), ^{13}C-urea breath test, *H. pylori* culture and histopathologic examination.

Measured outcome parameters

Early bleeding was defined as hematemesis or melena requiring emergent endoscopy before scheduled second-look endoscopy on POD 1, and delayed bleeding was defined as this after second-look endoscopy. Furthermore, bleeding of mucosal defects after ESD on second-look endoscopy was classified according to the Forrest classification using recorded images by an endoscopist (S.O.) who did not have information about delayed bleeding [8]. The incidence rate of delayed bleeding was analyzed, and patients' characteristics, clinicopathological diagnosis of neoplasia and perioperative records were compared to investigate risk factors related to bleeding of mucosal defects on second-look endoscopy.

Statistical analysis

Dr. SPSS for Windows version 11.0.1 J (SPSS Inc., Chicago, IL, USA) was used for data analysis. Summarized

numerical data were expressed as medians with standard deviation. Categorical data were compared using the χ^2 test, and numerical data were compared using Student's t test. Predictors with a significant difference as determined by univariate analysis were included in multivariate analysis by using logistic regression. A p value of <0.05 in each analysis was considered statistically significant.

Results

Incidence of delayed bleeding after ESD

Early bleeding occurred in two patients (0.45 %), and both of those patients were successfully treated with only endoscopic hemostasis. Intraoperative perforation occurred in six patients, and the scheduled second-look endoscopy was cancelled. One of those patients received a surgical operation because of pan-peritonitis. Second-look endoscopy was not performed in 27 patients because the scheduled day was on the weekend. There was no delayed bleeding in 33 patients who did not receive second-look endoscopy.

A total of 406 second-look endoscopies were performed, and delayed bleeding after second-look endoscopy occurred in 11 patients. Three patients were using regular antithrombotic agents. There was no significant difference between bleeding rates in patients with and those without second-look endoscopy (2.7 vs. 0 %, $p = 0.722$). Flow charts are shown in Fig. 1.

Active bleeding on second-look endoscopy and delayed bleeding (Fig. 2)

At scheduled second-look endoscopy on POD 1, active bleeding (Forrest Ia or Ib) from the iatrogenic ulcer was observed in 52 patients (12.8 %), and 12 (2.96 %) of those patients had coagula in the stomach. Spurting bleeding (Forrest Ia) was observed in two patients, and oozing bleeding (Forrest Ib) was observed in 50 patients. All of those patients were successfully treated with only endoscopic treatment, and no surgical intervention was required. Non-bleeding visible vessels (Forrest IIa) were detected in 34 patients, and 31 patients received preventive endoscopic hemostasis.

In 11 patients with clinical delayed bleeding, 4 patients were Forrest Ia or Ib (all of those patients had received endoscopic hemostasis on second-look endoscopy), and the incidence of delayed bleeding in patients with Forrest Ia or Ib was significantly higher than that in patients with Forrest IIa, IIb or III (7.69 vs. 2.02 %, $p = 0.0399$).

Details of patients with delayed bleeding after second-look endoscopy

Delayed bleeding from the same vessels after endoscopic hemostasis in the cases with Forrest Ia or Ib was observed in one patient, and three patients had other exposure vessels. These four cases needed a long ESD procedure time for severe intraoperative bleeding (mean procedure time: 112.5 min), and there was recurrence of delayed bleeding in two patients.

On the other hand, an exposure vessel was detected from a review of images on second-look endoscopy in only one patient without endoscopic hemostasis.

Predictive factors for active bleeding on second-look endoscopy

Active bleeding occurred in 12.8 % (52/406) of all patients who received second-look endoscopy. The background factors of those patients and features of gastric neoplasms were evaluated to find risk factors (Tables 1, 2, 3). Complication of a histological ulcer in the lesions, large size of the resected specimen and long ESD procedure time were shown to be risk factors by univariate analysis.

Multivariate analysis was then performed (Table 4), and large size of the resected specimen was identified as a risk factor for hemorrhage of mucosal defects after ESD. Table 5 shows odds ratios of active bleeding on second-look endoscopy according to the size of the resected specimen. Bleeding risk depended on the size of the resected specimen, and the odds ratio of a specimen size of >35 mm was 1.9 (95 % confidence interval: 1.052–3.42, p value: 0.036).

Discussion

Rates of delayed bleeding after gastric ESD did not differ greatly in previous studies, occurring in about 0–15 % of the patients [4, 5, 7, 9–11]. Delayed bleeding is controlled well by endoscopic hemostasis; however, urgent endoscopy should be avoided as much as possible. Second-look endoscopy is generally performed within several days after ESD, but the clinical benefits of second-look endoscopy including prevention of delayed bleeding have not been clarified [4].

Goto et al. found in their retrospective study that second-look endoscopy after ESD did not prevent delayed bleeding [12]. In that study, delayed bleeding occurred in 2.8 and 2.5 % of the patients before and after second-look endoscopy, respectively. On the other hand, Kim et al.

Fig. 1 Flow charts of delayed bleeding after gastric ESD. A total of 406 scheduled second-look endoscopies were performed. There was no significant difference between bleeding rates in patients with and those without second-look endoscopy (2.7 vs. 0 %, $p = 0.722$)
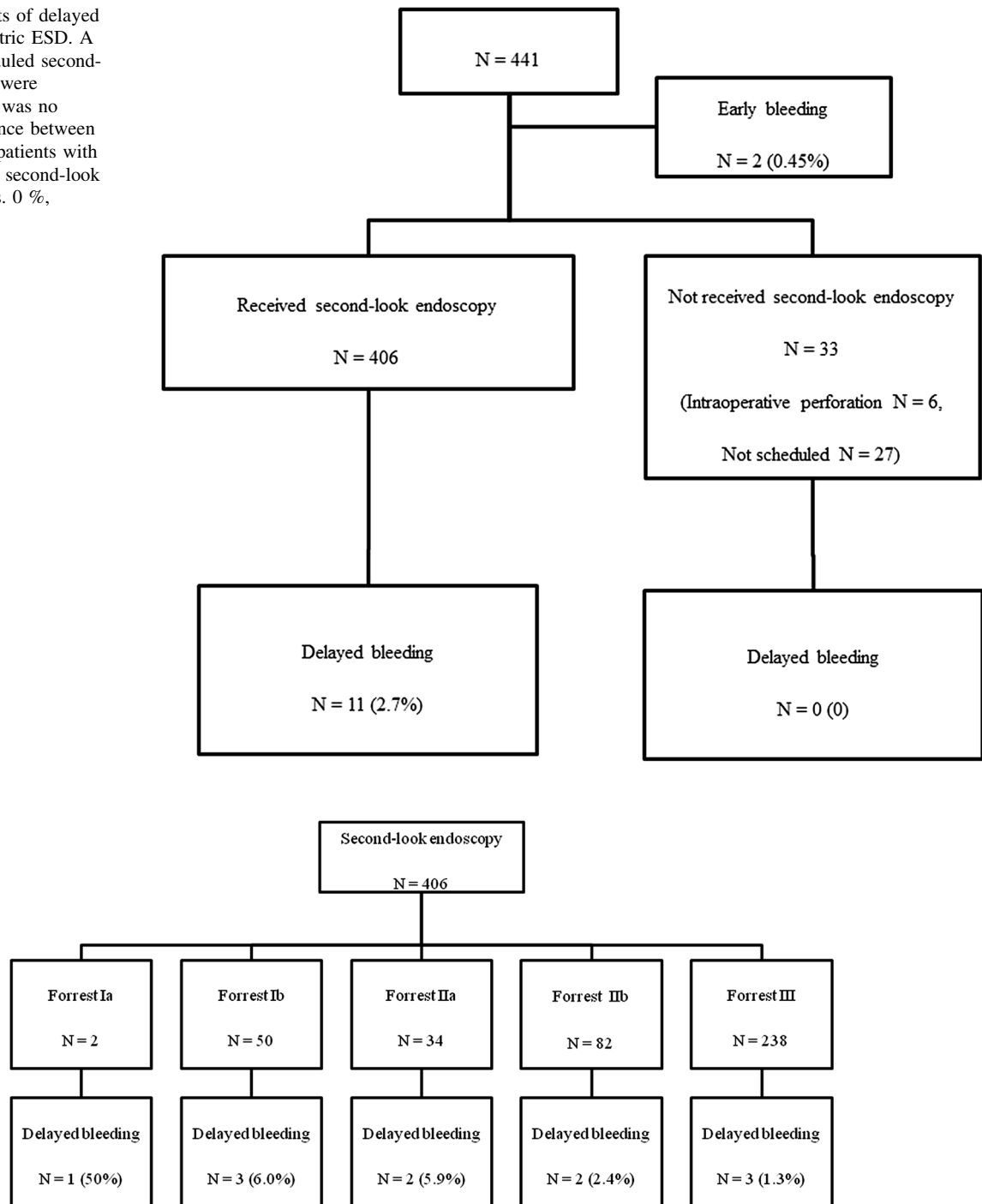
Fig. 2 Hemorrhage of mucosal defects after ESD on second-look endoscopy according to the Forrest classification and delayed bleeding. Spurting and oozing bleeding (Forrest Ia and Ib) were observed in 52 patients, and all of those patients were successfully treated with endoscopic hemostasis. Non-bleeding visible vessels (Forrest IIa) were detected in 34 patients, and 31 of those patients received preventive endoscopic hemostasis. The delayed bleeding rates in each group are shown

reported that delayed bleeding occurred in 2.0 % of their patients and that second-look endoscopy was useful for preventing delayed bleeding because of the much lower frequency of delayed bleeding after second-look endoscopy (0.23 %) [13]. We could not show these data because we performed routine second-look endoscopy, and we

therefore examined the relationship between delayed bleeding and hemorrhage of mucosal defects after ESD on second-look endoscopy.

Recently, there have been a few reports on prospective study of second-look endoscopy after gastric ESD [14, 15]. Ryu et al. reported that routine second-look endoscopy

Table 1 Characteristics of the patients according to the Forrest classification on second-look endoscopy

	Forrest Ia or Ib N = 52	Forrest IIa, IIb or III N = 354	p value
Gender (M/F)	38:14	271:83	0.757
Age, mean (SD*), years	71.2 ± 9.41	71.0 ± 8.69	0.443
Comorbidities (n)			
Ischemic vascular disease	7	49	0.941
Diabetes mellitus	9	54	0.715
Hemodialysis	0	2	–
Liver cirrhosis	0	9	0.612
Platelet, mean (SD), 10^4 μL	22.0 ± 5.42	21.7 ± 7.99	0.348
Creatinine, mean (SD) (mg/dl)	0.80 ± 0.30	0.85 ± 0.27	0.877
Positive for *H. pylori*[†], n (%)	24/45 (53.3 %)	199/310 (64.2 %)	0.187

* Standard deviation

[†] *Helicobacter pylori*

Table 2 Regular use of drugs by the patients according to the Forrest classification on second-look endoscopy

	Forrest Ia or Ib N = 52	Forrest IIa, IIb or III N = 354	p Value
Antithrombotic agents, n (%)	13 (25 %)	66 (18.6 %)	0.304
Aspirin	7	36	
Ticlopidine Hydrochloride	2	17	
Warfarin (Heparin bridging)	3 (2)	18 (9)	
Others	2	13	
Multiple combination	2	18	
Antacids (H_2RAs or PPIs*), n (%)	13 (23.1 %)	66 (17.5 %)	0.280

* Histamine receptor-2 antagonists or proton pump inhibitors

Table 3 Features of gastric neoplasia according to the Forrest classification on second-look endoscopy

	Forrest Ia or Ib N = 52	Forrest IIa, IIb or III N = 354	p value
Location of the lesions, n, L/M/U*	28/21/3	172/136/46	0.323
GC/LC/AW/PW[†]	14/22/7/9	73/150/49/82	0.673
Macroscopic depressed type, n (%)	33 (63.5)	218 (61.6)	0.879
Mixed histological diffuse type, n (%)	1 (1.92)	27 (4.24)	0.234
Submucosal invasion, n (%)	7 (13.5)	63 (17.8)	0.440
Complication of a histological ulcer, n (%)	7 (13.5)	17 (4.80)	0.023
Size of the neoplasm, mean (SD[‡]) (mm)	20.25 ± 16.3	16.6 ± 10.7	0.061
Size of the resected specimen, mean (SD) (mm)	37.7 ± 16.2	32.2 ± 11.8	0.011
ESD procedure time, mean (SD) (min)	103.5 ± 68.8	78.6 ± 53.4	0.008
En bloc plus R0 resection, n (%)	47 (90.4)	326 (92.1)	0.594

* *L* lower/*M* middle/*U* upper

[†] *GC* greater curvature/*LC* lesser curvature/*AW* anterior wall/*PW* posterior wall

[‡] Standard deviation

after ESD is not necessary based on the results of a prospective randomized trial [14]. However, in their trial, there was a relatively high rate of delayed bleeding (13.5 %), and more than half of the cases of bleeding occurred within 3 days after ESD. The rate of delayed bleeding in our institution was 2.71 %, and only 0.74 % of the cases (3/406) occurred within 3 days after ESD. About 3 % of the patients who received second-look endoscopy had coagula in the stomach and received endoscopic hemostasis before clinical delayed bleeding; therefore,

Table 4 Multivariate analysis of predictive factors related to active bleeding on second-look endoscopy

	Odds ratio	95 % CI*	*p* value
Size of the resected specimen (mm)	1.02	1.00–1.05	0.0436
ESD procedure time (min)	1.00	0.998–1.01	0.178
Complication of a histological ulcer	2.57	0.922–6.58	0.0700

* Confidence interval

Table 5 Odds ratios of active bleeding on second-look endoscopy according to the size of resected specimens

Size of the resected specimen (mm)	Odds ratio	95 % CI*	*p* value
>30	1.73	0.962–3.16	0.0670
>35	1.90	1.05–3.42	0.0336
>45	2.05	0.939–4.19	0.0702

* Confidence interval

endoscopic hemostasis on second-look endoscopy might reduce the incidence of delayed bleeding within several days after ESD.

From a Japanese multicenter prospective randomized controlled trial (the SAFE trial), Mochizuki et al. showed that second-look endoscopy did not contribute to the prevention of post-ESD bleeding, too [15]. Although active bleeding should be principally controlled on second-look endoscopy, non-bleeding visible vessels have to be treated prophylactically. It was shown in a previous study that preventive coagulation of visible vessels in the resection area at the end of ESD significantly reduced delayed bleeding [16]. However, delayed bleeding in the patients who received prophylactic hemostasis on POD 1 was more frequent than that in the patients who did not receive it in the SAFE trial. Interestingly, this was the same as our data. The rate of delayed bleeding after endoscopic hemostasis on second-look endoscopy in our institution was 6.02 %. We are not sure, but tissue damage after thermocoagulation may have contributed to the delayed bleeding.

Is second-look endoscopy routinely necessary for all patients after ESD? Our opinion is that it is not routinely necessary, in agreement with recently reports [14, 15], and we therefore have to select lesions for which second-look endoscopy is required. Analysis of risk factors for bleeding after ESD in previous studies showed that the location and size of the tumor and presence of an ulcer were independent predictive factors [17–19]. A long procedure time and use of drugs related to gastric injury or bleeding have also been shown to increase the incidence of delayed bleeding [5, 20]. Risk factors of lesions for which endoscopic hemostasis was performed on second-look endoscopy in the present study were similar to the risk factors in those previous studies; however, the only independent risk factor found in our study was the large size of the resected specimen. Although there has been no evidence that second-look endoscopy decreases the rate of delayed bleeding

after gastric ESD, the low incidence of delayed bleeding after second-look endoscopy and high rate of endoscopic hemostasis on second-look endoscopy might indicate the importance of second-look endoscopy.

The present study has several limitations in that it was a retrospective single-center study with a small number of cases, and discontinuation periods of antithrombotic agents were not followed to current consensus, since the study was before revision of the Japanese guidelines. A large-scale prospective study is needed to define lesions for which second-look endoscopy should be performed after gastric ESD.

In conclusion, active bleeding of mucosal defects after ESD on second-look endoscopy is a risk factor for clinical delayed bleeding, and it depends on the size of the resected specimen.

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